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# PROSPECTS IN PSYCHOPHARMACOLOGY[1]

HAROLD E. HIMWICH, M.D.

I appreciate greatly the honor you have bestowed upon me in the office of president. Among my duties is the presentation of the annual Presidential Address, a duty, which I am happy to have the opportunity to fulfill. The title I have chosen would have been impossible three short years ago (10). A new branch of science, long overdue, is now growing and revealing the early rapid development of the newborn—a newborn member of the family of medical sciences.

In seeking a title for this address I found that our terminology did not possess a term adequate to describe the new drugs for the treatment of behavioral disturbances. It is true that medications have been used for a long time for brain diseases, but now we are developing pharmacological agents that influence the mind as well. Against such a dichotomy between brain and mind we have the idea that any sharp delimitation between these two aspects of behavior is not possible; on the contrary, we have a continuous spectrum. For example, though we prescribe atropine and atropine-like drugs against Parkinsonism and the new tranquilizing drugs to mitigate hallucinations and delusions, atropine does affect the mind and can even bring on an organic confusion while Parkinsonism is one of the side reactions of the new drugs. Therefore, one term to include the entire gamut of such drugs would be preferable. The descriptive designation of neuropharmacology is acceptable. Yet on an operational basis, because some are more interested in the practice of neurology and others in psychiatry, it seemed advisable to use the name *psychopharmacology* to emphasize the new direction taken by pharmacology.

Pharmacological treatments for the mind are not new. They have been employed for a long time. In the past we have gradually developed methods to deal with disturbed, hallucinating and delusional patients. Barbiturates bring surcease to the patient and to the physician who attends him, but the results are relatively ephemeral. Electroshock is also widely used to maintain feasible interpersonal relationships in an otherwise disturbed ward. Now, however, violent patients can be managed in an open ward by methods which are less drastic than electroshock and with more enduring results than those of the barbiturates. The new pharmacological agents appear to be of a different order so that a term is now applied to drug action with new meaning, that is, *tranquilization* to connote sedation without hypnosis. Fabing has suggested the term *ataraxia*, denoting peace of mind, to describe the action of the new psychopharmacological agents (12).

What are these drugs? What have they accomplished? What are their mechanisms of action? What is in store for the future?

## Clinical Evaluation

The two new drugs have had many names attached to them, but the accepted generic nomenclature refers to them as chlorpromazine and reserpine.[2] Though the effects of these drugs are still under active investigation, we already have a considerable body of knowledge on the clinical actions of these drugs, and they will be referred to briefly.

[1] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

[2] The trademark of Smith, Kline and French Laboratories for chlorpromazine is Thorazine and that of Ciba Pharmaceutical Products, Inc., for reserpine is Serpasil.

Reports reveal that patients with schizophrenic reactions in catatonic or paranoid excitement, manic depressives in the hypomanic or manic stage, patients with agitated senile reactions, acute obsessive states, tension states and acute anxiety are helped by chlorpromazine (26, 29, 31, 56). In fact, a component of overactivity in the patient suggests a favorable usage of these drugs, and for that reason, the more disturbed the patient, the more dramatic are the results obtained with this tranquilizing drug. In contrast, patients with burnt out schizophrenic processes who are regressed and without active hallucinations and delusions are not as favorable subjects for this form of therapy (1). Nor are patients with depressive reactions without anxiety and tension, patients who suffer from chronic anxiety neurosis with extensive somatization likely to be helped (27).

In general, the same therapeutic delimitation has been reported for reserpine (30). Patients who had been assaultive, resistive, raving and denudative were so improved that they were able to return home (38). Disturbed, psychotic patients could be removed from maintenance electroshock treatment. Even some of those who had responded poorly to electroshock could be sent home after receiving reserpine (53).

The distinction between the results obtained on excited patients and those with apathy is again seen in the effects of reserpine on geriatric disorders (48). The proportion of elderly psychotic patients who were irritable, quarrelsome and apprehensive, revealing improvement on reserpine, was greater than that of the patients who showed chiefly depression, negativism, apathy and withdrawal. In fact, the chronic administration of reserpine may produce such untoward response as withdrawal, lethargy and unhappiness but not anxiety (17). Chlorpromazine, too, may evoke depression with obsessive features (1).

The advantages of these two drugs are not limited to the hospital and a greater number of discharged patients, but are also extended to the physicians' office because more psychotics can now be treated on an ambulatory basis. Neuroses have also been satisfactorily managed. Patients with stubborn anxiety and signs of tension are rendered relaxed and comfortable and are able to go about their daily duties with less effort. There are other than therapeutic advantages involved. Whether in private practice or in the hospital these treatments are less expensive than the standard ones, and the factor of economy is a large one. The highly trained personnel required by the standard treatments will form a smaller factor for consideration in the future. Among the benefits afforded by these drugs must be included a better atmosphere on the ward, affecting both patients and personnel.

My experience, gained in association with Doctors L. H. Rudy and F. Rinaldi, is concerned with approximately 40 patients on whom the effects of Frenquel,[3] a more recent advance, as well as of reserpine and chlorpromazine have been evaluated in turn on the same group of patients (46). At this time I would simply like to point out briefly some clinical differences among these three drugs, keeping in mind the fact that our conclusions apply to the small number of patients we have studied. Both reserpine and chlorpromazine were effective in the treatment of patients with paranoid reactions. We, however, regarded chlorpromazine as better for this clinical category and especially so because reserpine activated the symptomatology of two of our patients. In the tranquilization of patients with schizoaffective reactions chlorpromazine also appeared to be the drug of choice. On the other hand, the patients with hebephrenic reactions, as well as those with mixed hebephreno-catatonic reactions, benefited more from reserpine. Though the members of the last two groups exhibited better ward adjustment and management with chlorpromazine, they did so at the price of aggravation of the symptoms of withdrawal, apathy, passivity and seclusiveness. Similarly, reserpine produced an improvement in one patient with involutional depression, yet on chlorpromazine his condition became worse. Taking into consideration all the clinical categories we found that reserpine produced a greater number of improvements in our moderately disturbed and chronically ill patients.

Frenquel, too, was of value and induced beneficial effects on our patients with schizo-

[3] Frenquel is the trademark of the Wm. S. Merrell Co. for azacyclonol.

phrenia. Some of these belonging to the paranoid group revealed a moderation in the intensity of their hallucinatory and delusional experiences with resulting improvements of behavior. Ward adjustment became better as hostility and overactivity diminished.

More appropriate behavior was also observed in the hebephrenic and hebephrenocatatonic patients as their thought processes and speech became more comprehensible and logical while catatonic features were rendered less prominent in intensity and duration.

In a comparison of the effects of Frenquel with those of reserpine and chlorpromazine, a difference was noted in so far that one or the other of the latter two induced in some patients of each clinical category a degree of improvement greater than that attained by any patient under Frenquel. Thus the modifications of behavior induced by Frenquel were neither so extensive nor so marked as were those observed following the use of reserpine and chlorpromazine. Yet when weighing Frenquel on the balance, its greater safety and freedom from side effects are arguments in its favor. Certainly this tranquilizing drug was valuable in the treatment of our moderately disturbed and chronically ill patients.

## Physiological Analysis

Experience has taught us that drugs have multiple sites of action, each with different thresholds of susceptibility. This aphorism applies not only to the various organs of the body but also to the component parts of the brain. Though the final effect of a drug must be defined in terms of its integrated action on the entire body, yet for the sake of convenience the influence of chlorpromazine and reserpine on different brain structures will be considered separately.

The consensus in regard to both drugs is that they depress the hypothalamus, the portion of the brain which as demonstrated by Cannon and his students, notably Bard (2), contains the patterns for mobilizing the organism for the fight and flight reactions. In this area are found centers for the control of basal metabolism and temperature, the sleep-wakefulness cycle and blood pressure. In addition the hormonal balance is changed as the support afforded to the anterior pituitary gland is reduced by hypothalamic depression. The amount of gonadotrophic hormones released by the anterior pituitary is decreased (3), and for that reason menstrual disturbances are observed (28). The anterior pituitary is rendered less susceptible to stimulation, and that has an effect similar to that evoked by a lowered production of ovarian hormones, a phenomenon which brings on lactation (28). Chlorpromazine (8) influences hypothalamic functions in such a manner that basal metabolism is decreased and body temperature lowered. Blood pressure falls, and sleep is facilitated as barbiturates and other hypnotic and narcotic drugs are potentiated. Most important for the treatment of disturbed patients is the fact that the posterior hypothalamus, containing sympathetic centers, is so affected by chlorpromazine that patterns for emotional expression tend to be inhibited. The central action which serves to diminish blood pressure is greatly enhanced by the chlorpromazine blockade of the sympathetic ganglia. Heart rate is increased, in part due to an atropine-like action but also in response to a fall of blood pressure. This drug-induced fall of blood pressure, in addition to the depression of metabolism and of temperature, explains why chlorpromazine is an essential part of the hibernation cocktail (11). With a fall in basal metabolism temperature and blood pressure, the blood supply dwindles and operations are rendered relatively bloodless. Such a change, favorable for surgical procedures, should, however, be carefully controlled so that systolic pressure does not fall below 55 to 65 mm. Hg. For brain operations the patient should be kept in the Trendelenberg position as elevation of the head to reduce bleeding further can produce permanent cerebral damage.

Reserpine, like chlorpromazine, depresses hypothalamic mechanisms but in contradistinction to chlorpromazine does not exert direct effects on peripheral nerve structures (4). The inhibition of the sympathetic representation in the hypothalamus explains the fall in heart rate, the drop in blood pressure, the constriction of the pupils, and the increased intestinal activity. These parasympathomimetic effects, however, are not caused by peripheral stimulation of parasympathetic

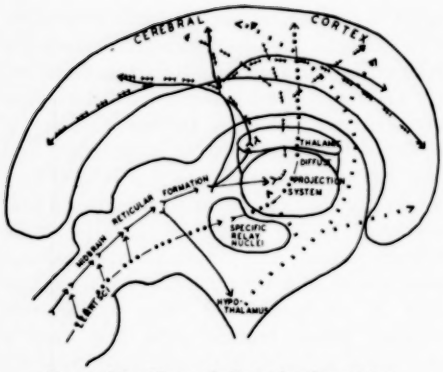


FIG. 1. Mesodiencephalic activating system

Stimuli from the periphery of the body evoke impulses which travel via the lemnisci through the specific relay nuclei of the thalamus and thence to specific sensory areas of the cerebral cortex. The lemnisci send collaterals to the mid-brain reticular formation, and by these paths impulses advance through that formation to the thalamic diffuse projection system, which in turn arouses the cerebral cortex in a diffuse manner. Collaterals from the mid-brain reticular formation also pass to the hypothalamus and carry impulses from that area by way of the diffuse system to the cerebral cortex.

nerves nor by peripheral inhibition of sympathetic nerves.

## NEUROELECTRICAL ANALYSIS

Dr. Franco Rinaldi and I, working on rabbits, reported another central site for the action of these drugs, namely the mesodiencephalic alerting sytem (41, 42). Historically this system is built up of two portions, the reticular formation of Moruzzi and Magoun (36) and the thalamic diffuse cortical projections of Jasper (24) (fig. 1). The two parts may, however, be regarded as acting together, and for brevity they will be termed simply the activating system. Probably collaterals from the lemnisci carry afferent impulses to the reticular formation. The hypothalamus is involved in the function of the activating system as the excitatory process is conducted from the reticular formation to the subthalamus and hypothalamus in turn and thence back to the cortex either directly (52) or via the thalamus (19). When this system undergoes stimulation, the alerting, arousal or awakening EEG pattern is produced. As, however, excitation diminishes or ceases, the sleep or drowsy pattern is observed. The drowsy pattern is characterized by slow waves of high amplitude interrupted by 14 per second spindles, and the alert pattern, by low amplitude rapid waves in the cortex between 20 and 30 per second as well as a continuous repetition of 4 to 7 per second waves in the thalamus (fig. 2). Not only is the arousal reaction evoked by nervous stimuli, but it is facilitated by central nervous system stimulants, for example, amphetamine or Meratran (fig. 3). In contrast, drugs inducing sleep like the barbiturates are associated with the drowsy pattern. An early effect of barbiturate depression is the development of high voltage fast frequencies, but the latter gives

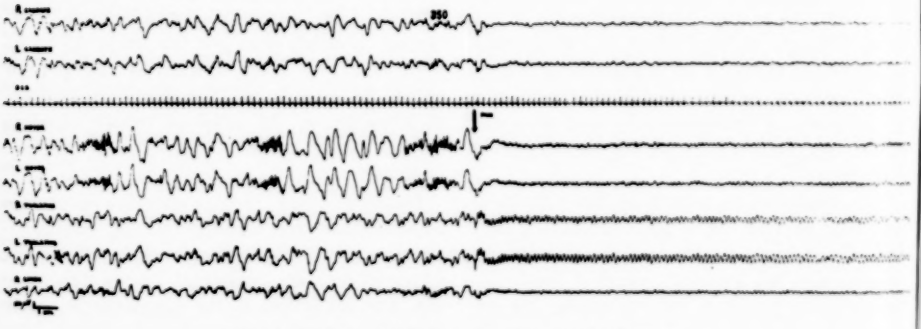

FIG. 2. Peripheral stimulation arouses activating system

An impulse from the periphery evoked by pain activates the alerting mechanism and changes the drowsy pattern to one of alertness. The left part of the figure reveals the resting pattern of high voltage slow waves and 14 per second spindles. The right part of the record shows cortical fast low voltage activity and 4 to 7 cycles per second rhythm of thalamic origin.

Records are derived bilaterally from the limbic cortex, the motor cortex, the caudate nucleus and the thalamus. In addition an ECG record is presented.

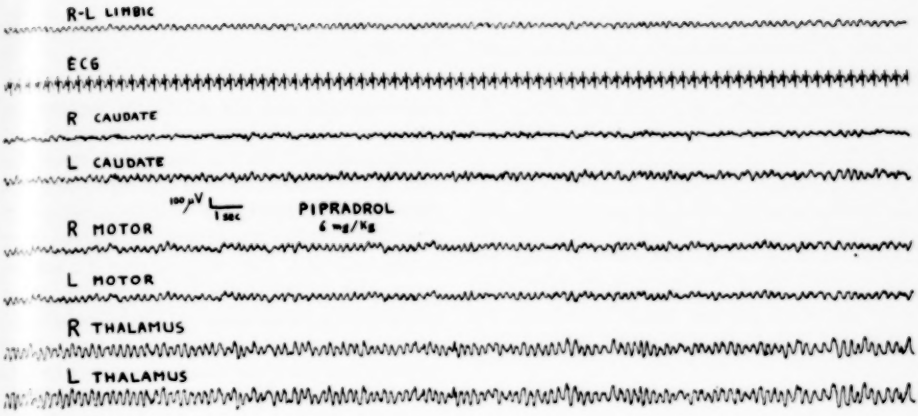


FIG. 3. Alert pattern evoked by Meratran (pipradrol)

The EEG pattern produced by 6 mg./kg. of Meratran (pipradrol) is essentially one of enduring alertness. A thalamic rhythm of 5 cycles per second is seen while low voltage fast activity is dominant in the motor cortex and the caudate nuclei.

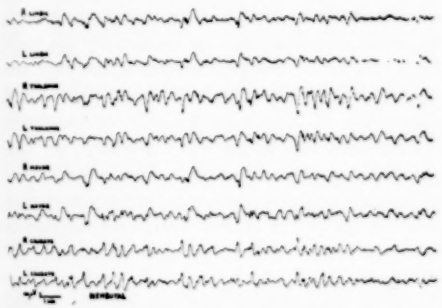

FIG. 4. Effect of moderately deep barbiturate depression on brain waves.

Slow, 1 to 3 cycles per second, waves become diffusely dominant over the entire record as the activating system is depressed by pentobarbital (Nembutal).

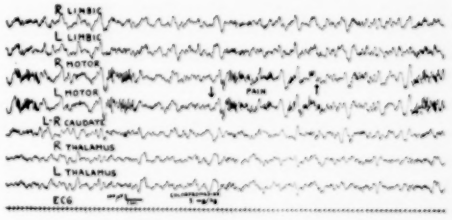


FIG. 5. Alerting effect of stimulus prevented by 5 mg./kg. of chlorpromazine.

Note the absence of the alerting reaction to pain due to comparatively low doses of chlorpromazine. Comparison with the control record (fig. 2) reveals the similarity of the chlorpromazine-produced pattern to the normal sleeping picture.

way to slow delta waves as presented in figure 4 (5). Though there are exceptions to the rule (43, 55), in general it may be said that behavioral arousal is associated with stimulation of this activating system and behavioral sleep with its depression. The effect of a pain stimulus to evoke the arousal reaction is seen (fig. 2), but chlorpromazine in small doses (43) blocks such a response. For example, the pain stimulus no longer is capable of producing the alert state. This drug therefore diminishes the inflow or stimuli to the cortex, and we observe an inhibitory action (fig. 5). Thus in addition to the depressant effect of chlorpromazine on the hypothalamus we find a second site for depression in the activating system. According to Gellhorn the latter is involved in a diminution of the affect (19).

Reserpine, in comparatively small amounts, stimulates this activating system (43, 44) (fig. 6). With doses of 0.5 mg./kg. or less little change is seen, from 0.5 to 1.0 mg./kg. alerting is facilitated, while from 0.5 mg./kg. upward a persistent alerting response is elicited. Even though the injection of reserpine was made into the carotid artery, arousal followed only after a latent period of from 20 to 30 minutes. This alerting response may be involved in the tranquilizing effect of reserpine. The same dose which depresses the hypothalamus may also stimulate the activating system, and thus the sleep which would be facilitated by hypo-

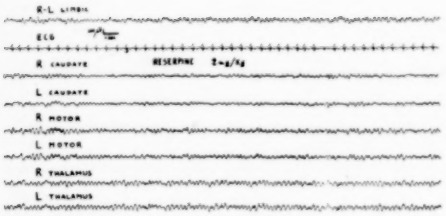


FIG. 6. Enduring alert pattern induced by reserpine

The resemblance of this picture to the normal alert pattern is due to the absence of high voltage slow activity and sleep spindles. Instead we observe low voltage fast waves in the cortex and a regular 4 cycles per second thalamic thythm. Note bradycardia induced by reserpine.

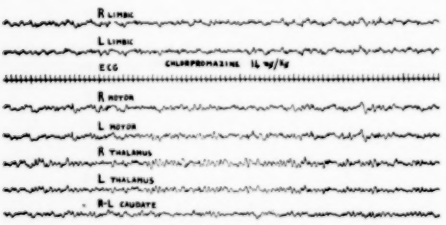


FIG. 7. Enduring alert pattern induced by large doses of chlorpromazine.

A continuous arousal pattern with low voltage rapid waves in the cortex and 5 cycles per second in the thalamus is observed.

thalamic depression is counteracted by the arousal reaction. Chlorpromazine, when given in large doses, also evokes the alerting response (43) (fig. 7). Thus in quantities greater than those required to depress the activating system chlorpromazine exhibits a reversal, and the activating system is stimulated. Large doses of chlorpromazine act like reserpine to evoke arousal.

A side reaction of the arousal state is the production of Parkinsonism (43, 44). As discussed by Magoun (33) the activating system possesses centrifugal effects as well as centripetal ones. The reticular formation and the reticulo-spinal tracts carry the main motor outflow of the extrapyramidal system. Experiments of Ward, McCulloch and Magoun (54) and of Folkerts and Spiegel (15) show that the overactivity of this system is responsible for the characteristic tremor of Parkinsonism. Stimulation of the activating system by these drugs may therefore produce a Parkinsonian picture just as well as by the liberation of this system from cephalad control due to lesions in the basal ganglia or the substantia nigra (15, 54).

Are the two central sites of action on the hypothalamus and the activating system the only cerebral areas influenced by reserpine and chlorpromazine? Such a statement would be rash in the present state of the rapid development of this subject. For reserpine, Schneider *et al.* find a facilitation of synaptic transmission in the cord (49). They suggest that if a similar facilitation occurs in the cortex, we may have an additional explanation for the hypothalamic depression induced by reserpine as the cortical inhibition of the hypothalamus is strengthened. For chlorpromazine, too, may augment the cortical inhibition exerted upon the hypothalamus (1).

I feel sure that we have not completely elucidated actions of these drugs on the brain. The importance of the activating system may not be limited only to the prevention of such hypnotic effects as can be evoked by the barbiturates or by the production of the side reactions of Parkinsonism. It is probable that depression of the hypothalamic sympathetic mechanisms mitigates the severity of the psychotic symptomatology. The present observations however, do not extend the action of these drugs to the cortex which presumably is involved in hallucinatory and delusional experiences. Still another site is suggested by Frenquel which does not depress the hypothalamus and yet appears to be effective therapeutically. In a group of patients with acute psychotic episodes, Fabing has obtained striking results (12). In our series of moderately disturbed delusional and hallucinatory patients we have also seen improvements.

How then are we to explain the salutary action of Frenquel on the psychotic patient? The only hints that we have are suggested by the observations of Fabing that Frenquel benefits model psychosis induced either by LSD (d-lysergic diethylamide) or mescaline (13). In animal experiments we observed that LSD or mescaline induced the arousal reaction. This is not characteristic of hallucinogenic drugs only because many central nervous system stimulants like amphetamine and Meratran (fig. 3) can also evoke the arousal responses (43). When Frenquel is injected subsequent to either amphetamine or Meratran, it does not reverse the arousal response, but

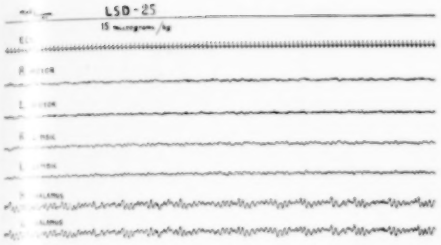


FIG. 8. LSD evokes alert EEG pattern

The abnormal pattern induced by LSD presents fast low voltage activity and 4–6 cycles per second thalamic waves.

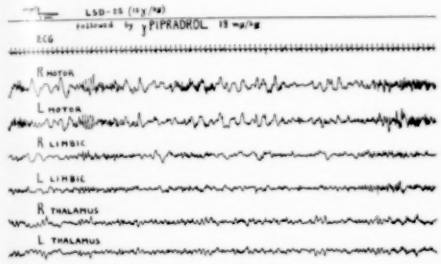


FIG. 9. Frenquel (gamma-pipradrol) eliminates abnormal EEG pattern induced by LSD.

The slow waves and 14 cycles per second spindles, abolished by LSD (see fig. 8), reappear on the normal drowsy electrical pattern restored by Frenquel (gamma-pipradrol).

when Frenquel is administered after LSD or mescaline, the alerting reaction is eliminated from the EEG and the resting pattern is restored (45) (figs. 8 and 9).

The lead afforded by Frenquel is suggestive because the low amplitude rapid frequency waves produced by LSD and mescaline are also found in untreated human subjects. Though such waves have been reported in but few so-called normal individuals, they occur in about one-third of the patients with schizophrenia, manic-depressive reactions, psychoneurosis, and in more than half of the patients with involutional psychosis they exhibit such waves (6, 9, 14, 37, 39). The mechanism for bringing about this low amplitude fast activity is unknown. It may be due in the first place to a disorder of the cerebral cortex. Another suggestion is that it represents the effects of an overactive alerting system upon the cortex. It is hardly likely that a peripheral stimulus is the cause of such overactivity. We must therefore seek for a central site in some structure of the brain, perhaps in the cerebral cortex. Under such conditions we might have a positive feedback. Not only does the cortex stimulate the activating system, but the activating system in turn stimulates the cortex, and so we have a vicious cycle. One way to test such susceptibility is to administer Frenquel to patients with low amplitude fast activity and see whether or not it can be eliminated. If Frenquel is successful in reducing fast activity, it may not be impossible that there is an association between the electrical hyperactivity of the brain and the psychotic process and that both are inhibited by the action of Frenquel.

## Neurochemical Analysis

I have briefly reviewed some of the behavioral results obtained by the use of Frenquel, reserpine and chlorpromazine. The alterations produced by these drugs, the clinical improvements, are explained in part by the observations made on animals as well as human subjects, including such pharmacological effects as depression of hypothalamic mechanisms. The observations made with the aid of the EEG were also helpful, for they disclose additional aspects of drug action on the activating system. But what are the biochemical changes which are the source of the pharmacological actions inducing alterations in behavior? Experiments of Grenell and associates (20), (22) revealed that when chlorpromazine was injected into rats and brain tissue was analyzed, changes in oxidation of the excised cerebral tissues were not observed. These results are in agreement with others on cerebral metabolic rate obtained in the human subjects who had received reserpine (21) or chlorpromazine (35). However, a significant alteration was observed in excised cerebral tissues, an accumulation of energy rich phosphates in the form of adenosinetriphosphate (ATP) (6). This accumulation could be due either to the accelerated production of ATP or its slower utilization. According to the authors the latter is the correct interpretation. It may be of some importance that the midbrain region of the rat containing the thalamus and hypothalamus showed a greater increase of ATP than any other cerebral part as a result of chlorpromazine.

The next step in our inquiry is to determine the cause of these changes in brain metabolism,

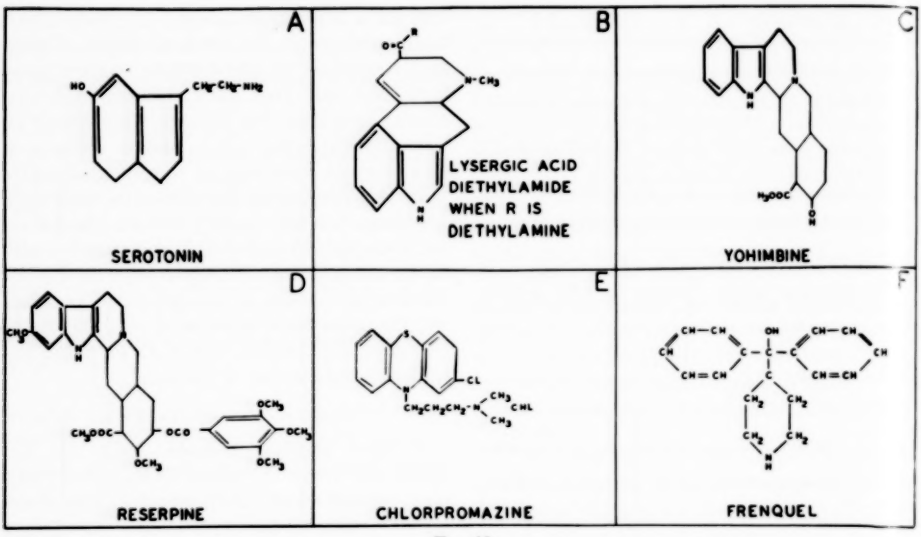


FIG. 10

A. Formula for serotonin. Note indole nucleus and 2-carbon side chain terminating in a nitrogen containing group.

B. Formula for LSD (d-lysergic acid diethylamide). Observe indole group and part of side chain similar to that of serotonin, represented by thickened lines.

C. Formula for yohimbine. The similarity of yohimbine to serotonin is apparent.

D. Formula for reserpine. Note striking similarity in the chemical structure of this tranquilizing drug to that of yohimbine.

E. Formula for chlorpromazine.

F. Formula for Frenquel. The chemical structures of the two tranquilizing drugs, chlorpromazine and Frenquel, differ from those of the four preceding substances. This figure is a modification of that presented by Woolley and Shaw (57).

and the answer to this question may involve the neurohormones of the brain. In that regard the experiments of Hoffer, Osmond and Symthies (23) on a breakdown product of adrenaline should be considered. These workers observed that a substance contained in a pink or deteriorated adrenaline solution evoked hallucinations. They believe that the hallucinogenic substance includes the indole nucleus as part of its chemical structure, and also pointed out that some hallucinogens like LSD, harmine, medmain, yohimbine contain this indole nucleus (fig. 10). In fact, Rinkel *et al.* have suggested that LSD may influence the enzyme system concerned with the metabolism of adrenaline (47). Marrazzi and Hart (34) as well as Liddell and Weil-Malherbe (32) emphasize disturbance of an adrenergic neurohumoral mechanism. Woolley and Shaw (57) were also struck with the similarities in the chemical structure of the hallucinogens, but their viewpoint was somewhat different as they stressed the resemblance to the neurohormone serotonin (5-hydroxytryptamine) found in smooth muscle as well as in the brain. They suggest that these pathogenic substances act as antimetabolites, combine with the same receptors as serotonin, but prevent the normal response elicited by serotonin. In addition, evidence in a paper by Shore, Silver and Brodie (50) reveals that serotonin in large doses is sedative and potentiates the action of Evipal, an ultrashort-acting barbiturate, in mice. This central action of serotonin is blocked by pretreatment with LSD (51), thus implicating serotonin in brain function and lending support to the suggestion of Woolley and Shaw that abnormal mentation is due to the blocking of serotonin receptors. Reserpine, like serotonin, potentiates Evipal (50), an action also prevented by LSD. Reserpine, which resembles serotonin in chemical structure (fig. 10), causes the liberation of serotonin. The evidence for this conclusion was obtained partly on dogs, for reserpine increased

their urinary excretion of a metabolic product of serotonin, namely 5-hydroxyindoleacetic acid (5 HIAA) (51).

Further experimentation showed that reserpine has a bi-phasic action on serotonin, not only an early and temporary increase but also a late and enduring diminution (40). Perhaps the continued injections of reserpine would prevent serotonin from attaining normal values, and in that case the benefit derived from reserpine lies in a decrease of serotonin. If these results yield a clue to the action of reserpine on the brain, and this is yet to be proved, then I would like to offer a tentative explanation for the therapeutic effects of reserpine, namely, that the abnormal activity of disturbed psychotic patients is associated with an excess of serotonin and that under continued dosage of reserpine the concentration of serotonin in the brain is reduced. In accordance with this speculation the lag in the clinical effects produced by reserpine represents the time necessary for the elimination of serotonin from the body and perhaps lowering its concentration in the brain. Furthermore, the continued pharmacological action of reserpine after that drug is withdrawn may indicate the period necessary for the restoration of the serotonin depots.

It is of interest that both chlorpromazine and Frenquel potentiate Evipal though Frenquel is weaker than chlorpromazine in this regard. The administration of chlorpromazine does not, however, increase the excretion of 5 HIAA. It would appear that these drugs act like serotonin. They are serotoninmimetic and go to the same receptors as serotonin, thereby reducing the effectiveness of that neurohormone. This viewpoint is the opposite of Woolley and Shaw (57) and suggests that abnormal mentation is associated with an excess of serotonin while a reduction in the concentration of serotonin is therapeutically beneficial.

Recent experiments, performed in our laboratory by Dr. E. Costa (7), have yielded additional evidence for such a conception. Using the rat uterus as a test object he observed that the uterine contraction produced by serotonin is blocked by each of the three tranquilizing drugs. The block evoked by Frenquel is of shortest duration, that induced by chlorpromazine lasts for a longer time, while the effect of reserpine is the most enduring of the three. Perhaps that is the reason why reserpine is the most effective of the three agents in causing the release of serotonin and the excretion of 5 HIAA. Furthermore, Dr. Costa has found that LSD and mescaline potentiate the uterine contraction caused by *minimal* doses of serotonin. This observation does not contradict that of Gaddum and Hameed (18) who found that LSD inhibits the *maximal* contraction induced by serotonin. Thus, at least for the rat uterus, the three tranquilizing drugs reduce the effect of serotonin, while in contrast LSD and mescaline augment its action. Though these experiments are suggestive, their significance in regard to the function of the brain will require further work.

## The Future

What has the future in store? Before making an attempt to define the paths of further progress, it is well to examine our present position. Most physicians who have tested these drugs are convinced that they are a great step forward. The beneficial effects are not a "flash in the pan" but have been widely corroborated. We can therefore look with satisfaction at the progress we have made. Do we cure our patients? Until we have unearthed the roots of schizophrenia, the answer to this question remains a semantic one. But now the psychiatrist has at his command drugs which are of aid in wiping out the symptoms of psychotic patients just as the internists can use insulin for the elimination of the symptoms of diabetes.

Added to our armamentarium are drugs which aid in the control of disturbed psychotic patients. These drugs are effective not only for disturbed patients with psychomotor overactivity but also for emotionally tense ones with acute anxiety. The value of these drugs is being tested for various clinical categories, and in general one might predict that in many conditions for which bromides were formerly used and now barbiturates are prescribed, the new drugs will receive preference (16, 25).

Therapeutic evaluations reveal that they are not the complete answer for our problem. All these drugs are tranquilizers. Though they are used successfully against depression associated with anxiety and tension, we still await the pharmacological agent that is as effective

as electroshock for melancholia. The plans for the immediate future also involve a consideration of some of the inadequacies of these drugs. Both chlorpromazine and reserpine exhibit undesirable side reactions, and efforts are now being bent toward their alleviation.

More important is the observation that not all patients were helped equally by any one of these three drugs and those of some clinical categories are benefited more than others by each of them. The discovery of additional pharmacological agents therefore becomes imperative. The suggestion from reserpine and chlorpromazine that drugs must depress the hypothalamus to be effective should be considered as it is apparent that such a depression will mitigate the severity of emotional expression both in somatic and mental terms. A second site of action is found in the activating system. Frenquel suggests the possibility of still other loci. One way to attain this goal of discovery of new therapeutic agents is indicated by past experience. Variation in chemical structures of the drugs now used may induce new and unexpected actions, and such variants should and will be evaluated clinically. But drugs of entirely different chemical constitution must be produced, perhaps with specific affinities for the receptors of neurohormones in the brain. Recent evidence from Brodie's laboratory, as well as our own, indicates that the tranquilizing drugs alter behavior by their influence on serotonin.

We are living in a moment of excitement, rich in potentialities that can be realized by increased interaction between psychiatrists and pharmacologists. We cannot help but feel that the advances made by chlorpromazine and reserpine, important as they are, represent only the initiation of a new era in psychiatry. The advent of Frenquel may be regarded as another harbinger of such an era. The science of psychopharmacology has come to stay!

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# THE CEREBRAL ELECTROGRAPHIC CHANGES INDUCED BY LSD AND MESCALINE ARE CORRECTED BY FRENQUEL[1, 2]

FRANCO RINALDI[3] AND H. E. HIMWICH

LSD (d-lysergic acid diethylamide), an alkaloid derived from ergot, produces in human subjects mental disturbances consisting of visual hallucinations and other psychotic symptoms. This phenomenon has been widely investigated because the LSD-evoked symptoms are similar to those of schizophrenic patients (1, 8, 12, 20, 23, 31, 34, 42, 44, 46, 47). Mescaline is another alkaloid long known to produce hallucinations and other psychological and somatic changes like those caused by LSD (2, 23, 31, 34). LSD affects the electrical activity of the brain of experimental animals and of human beings, diminishing or eliminating the slower rhythms, increasing the average frequency, introducing fast low voltage activity as well as causing a general diminution of voltage (3, 5, 13, 14, 22).

Frenquel (alpha-4-piperidyl benzhydrol hydrochloride) is a new non-hypnotic drug that renders animals less active (4) and is being applied in clinical psychiatry with promising results in the treatment of some psychiatric conditions (17, 41). Recently Fabing (17) reported that the psychotic symptomatology produced with LSD in human subjects could be corrected by the administration of Frenquel.

In our experiments on rabbits we studied the cerebral electrical activity of different brain structures as modified by LSD and mescaline, as well as by the subsequent administration of Frenquel.

## METHODS

All our experiments were performed in unanesthetized, curarized rabbits maintained by artificial respiration. For recording the electrical activity of the brain, openings of a proper size to hold firmly coaxial electrodes were made in the skull. The surface of the stainless steel outer electrodes was in contact with the dura. The inner electrodes, made of stainless steel needles covered with insulating varnish except at the tip, penetrated the brain for recording from subcortical structures. Eight such electrodes were placed; the surface electrodes recorded from the motor and limbic areas of both sides of the cortex, and the deep electrodes from the head of the caudate nuclei and the medial thalamus. Another bipolar coaxial stimulating electrode of stainless steel with a distance of 2 mm. between the two bare tips was placed in the medial reticular substance of the midbrain at the level of the anterior quadrigeminal body. Methods and coordinates for the placement of such electrodes were previously described (38). The intracerebral electrode tract and the site corresponding to the tip of each subcortical electrode were checked by means of serial sections of the whole brain according to the staining technique previously described (38).

Cerebral electrical activity was recorded by means of an 8 channel electroencephalographic instrument, Grass D-3; one channel being used for recording the ECG. A Grass stimulator model S-4 was employed for electrical stimulation of the midbrain reticular formation. Parameters for stimulation of that formation and its effects on cerebral electrical activity were described in detail in a previous publication (38).

The drugs employed in this study were as follows: d-lysergic acid diethylamide (LSD-25) 0.1% solution, Sandoz Chemical Works, Inc.; alpha-4-piperidyl benzhydrol hydrochloride (Frenquel), The Wm. S. Merrell Co.; atropine sulfate 1.0% solution; chondodendron tormentosum extract, purified (Intocostrin), E. R. Squibb and Sons; mescaline sulfate, S. B. Pennick and Co.; isofluorophate (DFP); d-, l-amphetamine sulfate, Smith, Kline and French; alpha-2-piperidyl benzhy-

[1] Frenquel is the trademark for azacyclonol of The Wm. S. Merrel Co., Cincinnati, Ohio.

[2] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

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drol hydrochloride (Meratran), The Wm. S. Merrell Co.; pentobarbital sodium (Nembutal), Abbott Laboratories; Chlopromazine hydrochloride (Thorazine), Smith, Kline and French.

All drugs were administered intravenously.

## Results

The control electrical activity of the brain of rabbits in our experimental conditions exhibited an alternation of two main patterns which are illustrated by the records in figure 1. The left section of the record shows the resting or sleeping pattern which is present as long as the animal is left undisturbed and resting quietly. It consists of slow (1–3 cps.) high voltage waves and spindles of 14 cps. waves more prominent in the motor cortex. In the thalamus a 2–3 cps. activity appears mixed with 6 cps. waves. An accidental or purposely-induced sensory stimulus such as sound, touch or pain, or an electrical stimulation of the brainstem reticular formation breaks up the resting pattern, replacing it by the alert one. In the record of figure 1 the alerting response (right section of the record) was elicited by direct electrical stimulation of the midbrain reticular formation (unidirectional square pulses of a frequency of 300 cps., 2 milliseconds duration, an intensity of 1.5 v. for a period of 1.5 seconds). The alert pattern consists of a 7–4 cps. rhythm of maximal amplitude in the leads from the medial thalamus, but is also apparent in the cortical leads. Caudate and cortical activities are characterized also by low voltage fast activity (20–30 cps.).

LSD was administered in progressively increasing amounts from 1 to 60 gamma/kg. With amounts of the drug between 1 and 5 gamma/kg. an increasing facilitation of the pattern of alerting responses was observed. Minimal accidental noises were sufficient to induce an alert record, and the threshold of electrical stimulation of the reticular formation was slightly lowered. Larger doses between 10 and 15 gamma/kg. enforced this effect so that finally all features of sleep (slow waves and spindles) were abolished and the record exhibited only the characteristics of an enduring electrographic alertness (fig. 2). This pattern persisted for a period of 1½ hours. By the use of still larger doses of LSD we observed a phenomenon which so far has remained unnoticed. Large amounts (20–60 gamma/kg.) reversed entirely the electrographic picture so that the slow waves and sleep spindles reappeared and persisted. With these larger doses it was also observed that the production of the electrographic arousal required stronger sensory stimulation and that the electrical threshold of the reticular formation was perceptibly increased. However, no complete block of the alerting response was ever observed even with the administration of 100 gamma/kg., a dose given to 3 animals only.

The administration of mescaline produced

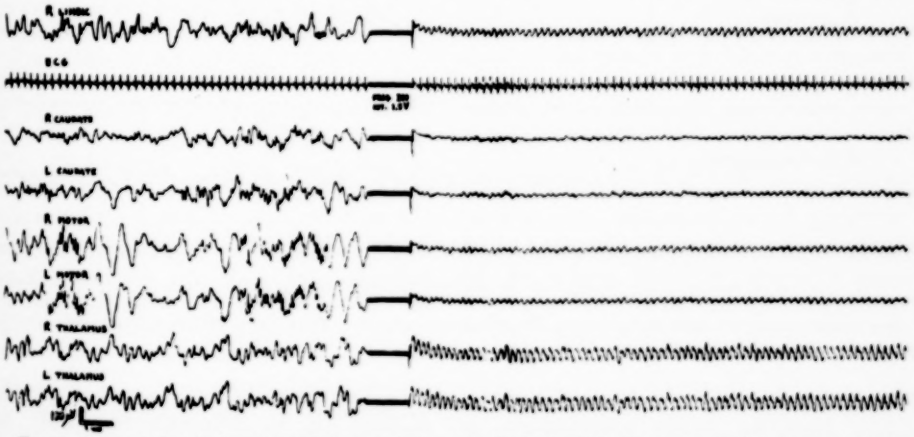


FIG. 1. Cerebral electrical activity of the curarized unanesthetized rabbit. The leads are (from the top tracing to the bottom one): (1) right limbic cortex, (2) ECG, (3) right caudate nucleus, (4) left caudate nucleus, (5) right motor cortex, (6) left motor cortex, (7) right thalamus, (8) left thalamus. (See description in text.)

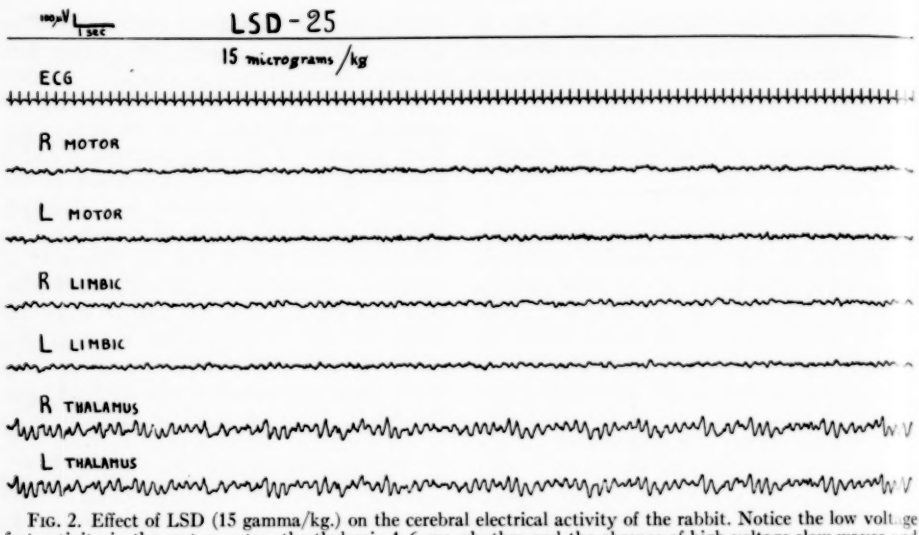


FIG. 2. Effect of LSD (15 gamma/kg.) on the cerebral electrical activity of the rabbit. Notice the low voltage fast activity in the motor cortex, the thalamic 4–6 cps. rhythm and the absence of high voltage slow waves and of spindles. The leads are (from the top tracing to the bottom one): (1) ECG, (2) right motor cortex, (3) left motor cortex, (4) right limbic cortex, (5) left limbic cortex, (6) right thalamus, (7) left thalamus.

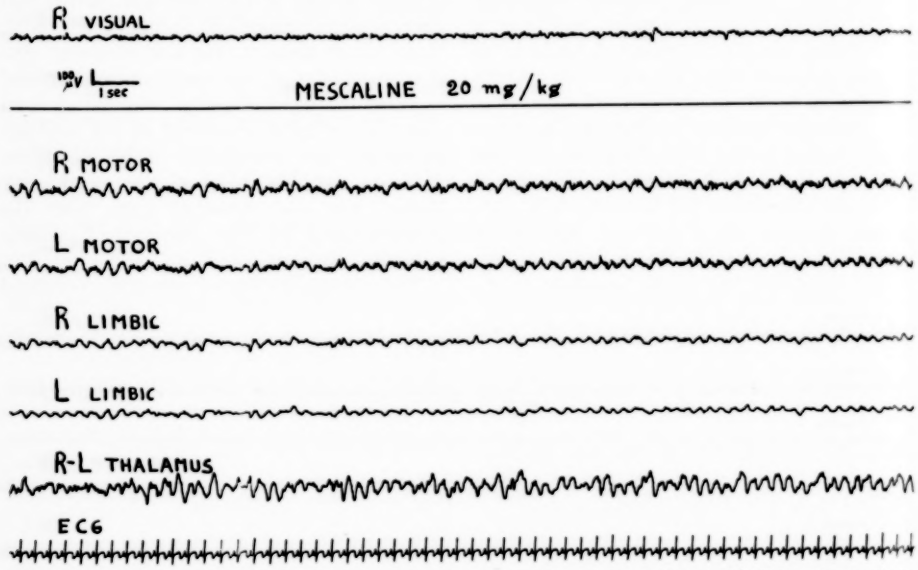


FIG. 3. Effect of mescaline (20 mg./kg.) on the cerebral electrical activity of the rabbit. Notice the similarity of this picture with that induced by LSD (fig. 2). The leads are (from the top tracing to the bottom one): (1) right visual cortex, (2) right motor cortex, (3) left motor cortex, (4) right limbic cortex, (5) left limbic cortex, (6) right-left thalamine (bipolar), (7) ECG.

changes similar to those of small doses of LSD. Mescaline given intravenously in amounts between 5–10 mg./kg. evoked an electrographic picture of alertness with the disappearance of the slow waves and spindles of sleep (fig. 3). Differently from LSD, no reversal of the alert pattern was observed with still larger doses of mescaline.

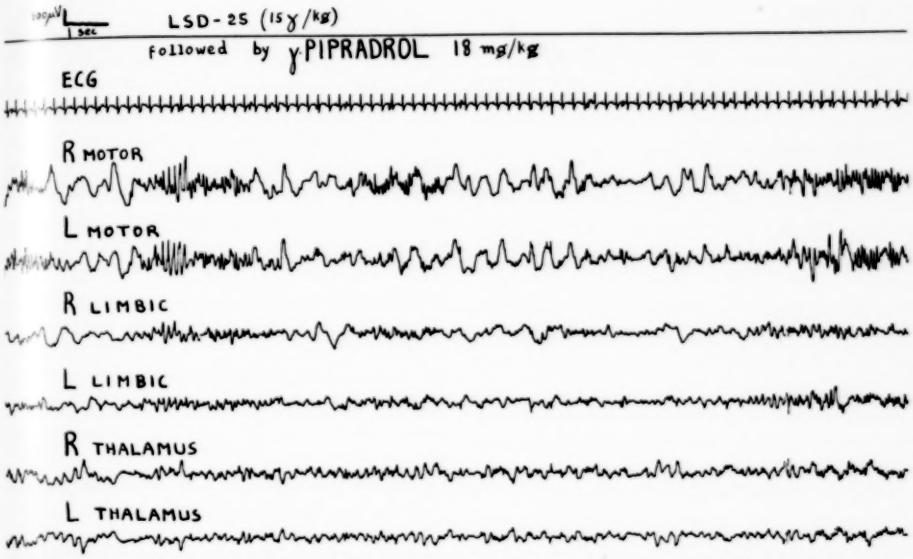


FIG. 4. Correction of the changes induced by LSD in the cerebral electrical activity of the rabbit by the administration of Frenquel (indicated in the figure as gamma-pipradrol). Notice the restoration of the spindles and slow waves typical of the resting pattern. Leads as in figure 2.

As soon as the alerting effect of the hallucinogenic drugs was fully developed, Frenquel was administered i.v. in progressively increasing doses from 1 to 30 mg./kg. It was observed that in amounts of 15–20 mg./kg. Frenquel corrected the electrographic changes induced by LSD (10–15 gamma/kg.), restoring the spindles and slow waves (fig. 4). With somewhat larger amounts (15–25 mg./kg.) Frenquel also eliminated the alerting effect of mescaline thus causing the sleep pattern to reappear (fig. 5).

The action of hallucinogenic drugs in producing an electrographic pattern of alertness is not a specific one. In fact a number of drugs give rise to a similar phenomenon. First will be listed cholinergic drugs, such as DFP, which stimulate specifically the mesodiencephalic activating system, the structure responsible for the production of the electrical alerting responses (38, 39). Other drugs that arouse electrical alertness are CNS stimulants like amphetamine and Meratran (40). Because of this lack of specificity for the changes induced by LSD and by mescaline, it seemed necessary to determine whether the corrective action of Frenquel was also non-specific. We therefore administered Frenquel in the same amounts and with the same technique, as in the experiments with the hallucinogenic drugs, to animals which had received doses of DFP (0.2 mg./kg.), of amphetamine (10 mg./kg.), or of Meratran (6 mg./kg.), sufficient to produce a permanent pattern of alertness similar to that caused by the hallucinogens. But Frenquel in any dosage failed to correct or to modify the electrical picture induced either by DFP, amphetamine or Meratran.

Previous work (40) showed that Frenquel alone, in the dosage with which it corrected the effects of hallucinogenic drugs, did not modify the spontaneous brain electrical activity of unpremedicated animals, for it did not enforce slow waves and spindles typical of the resting pattern, nor prevent the alerting response to physiological stimuli. Other drugs, unlike Frenquel, have the property of depressing the alerting mechanism and introducing the resting electrographic picture. First may be listed atropine (38, 39) which specifically paralyzes the mesodiencephalic activating system. Chlorpromazine is another drug which in small doses acts on the brain electrical activity as does atropine (40). Barbiturates, such as pentobarbital, also impose

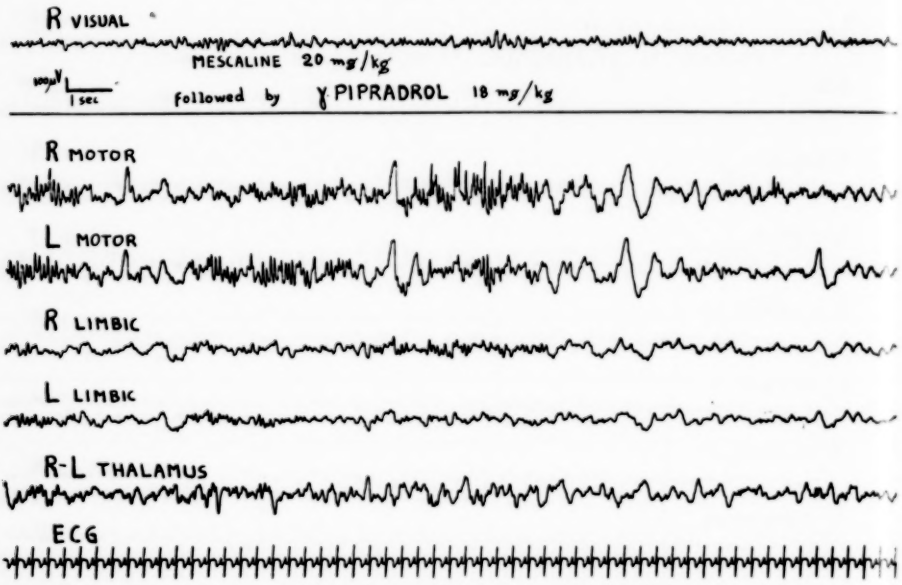


FIG. 5. Correction of the changes induced by mescaline in the cerebral electrical activity of the rabbit by the administration of Frenquel (indicated in the figure as gamma-pipradrol). Notice the restoration of the spindles and slow waves typical of the resting pattern. Leads as in figure 3.

the electrographic sleeping pattern (37). These three drugs in appropriate amounts eliminate the picture of alertness produced either by DFP, amphetamine or Meratran. Similarly either atropine (3 mg./kg.), Chlorpromazine (3 mg./kg.) or pentobarbital (15 mg./kg. i.p.), administered after the hallucinogenic drugs, corrected the pattern of alertness produced by LSD or mescaline, restored the features of sleep and depressed the arousal response to physiological stimuli.

Because LSD evoked a reversal in action when passing from small to large doses, we tested the influence of Frenquel after large doses of LSD. But after such doses of LSD as 20–60 gamma/kg. Frenquel did not change the cerebral electrographic pattern which remained a resting one.

## DISCUSSION

The alert electrographic pattern caused by the hallucinogenic drugs in our experiments is concordant with the observations of other authors in animals and in man. Delay and coworkers (13) observed in the rabbit that LSD produced a flattening of the electrographic record due to the disappearance of the higher voltage components. A similar phenomenon was observed in cats by Elkes and associates (14) who furthermore reported that in cats LSD completely abolished the sleeping electroencephalographic features of moderate barbiturate anesthesia (without changing the behavioral anesthesia). Our experiments with LSD showed clearly that the flattening of the electrographic record was not due to a disappearance of cortical electrical activity but rather to the long lasting presence of a pattern of alertness, practically indistinguishable from the normal one (fig. 2). Since the waves of the alert pattern are all of very low amplitude, at least in the corticogram, it is obvious that the immediate impression is that LSD flattens the cortical record.

It is known that the disappearance of the slow rhythms of sleep and the introduction of the alert pattern are due to the activity of a brainstem mechanism with diffuse projection over the entire cortex, the mesodiencephalic activating system (MDAS), which includes the brainstem reticular formation of Moruzzi and Magoun (32) and the thalamic diffuse projection system of Jasper (24). The MDAS

is excited physiologically by impulses coming from collaterals of the sensory lemnisci and branching into the brainstem tegmentum. The excitation of the MDAS can also be produced experimentally by direct electrical stimulation of the cephalad portion of the brainstem reticular formation as in our experiments. Following the stimulation of the MDAS a diffuse desynchronization of the activity of the cerebral cortex occurs, wiping off the slow rhythms of sleep and introducing cortical fast low voltage and a 4–7 cps. thalamic rhythm (fig. 1). The desynchronization of the corticogram is supposed to subserve the state of alertness and also to afford a background of cortical activity or cortical tonus which probably is of importance in the regulation of the level of consciousness, awareness and mental activity. Many drugs can produce electrographic patterns of alertness, and some of them stimulate the MDAS directly. Such a direct effect has been established for the cholinergic drugs like DFP (38, 39). In the case of the alertness evoked by such hallucinogenic drugs as LSD it is not known whether a direct effect on the MDAS is involved. In fact observations of Elkes *et al.* (14) cast a well-founded doubt upon this hypothesis. They observed that LSD is unable to desynchronize the cortical activity in the "encephale isole" sleep pattern. This suggests that the alert picture produced by LSD in the normal animal is not due to a direct action as the MDAS but rather to an increased inflow of alerting stimuli to that formation by a mechanism not yet determined. In any case it remains a fact that in the normal animal the activating mechanism appears overactive with LSD in amounts from 5 to 15 gamma/kg., dosages comparable to those producing a psychotic-like state in man. The observations on the action of LSD on the EEG of humans are also concordant with the findings in animals. Rinkel and coworkers (42) observed mild electrographic changes due to the administration of LSD in normal and psychotic patients consisting in an increase of a few cps. of the alpha frequency, together with diminished responsiveness to hyperpnea, which means interference with the production of slow high voltage waves characteristic of hyperpnea. Gastaut and coworkers (22) studied human volunteers and noted that LSD accelerated the alpha rhythm, while decreasing its amplitude and regularity. In addition low voltage fast rhythms similar to the beta frequency appeared in the central regions of the skull and at times became generalized. Bradley and coworkers (3) studied the responsiveness of the alpha rhythm to eyes opening and to light stimuli. These authors found that normal human volunteers who before the administration of LSD exhibited poor or no responsiveness to eyes opening and to attention, that is to say poor desynchronization, presented a ready desynchronization after LSD, together with a decrease in the amplitude of the alpha waves.

It is interesting to note the analogy between the EEG alterations induced by the hallucinogenic substances and the records often obtained from schizophrenic and other psychotic patients (6, 9, 10, 11, 15, 18, 19, 26, 27, 28, 29, 33, 35, 43). We refer to the "choppy" rhythm and similar low voltage fast records accompanied by poor alpha organization first described by Pauline Davis (9, 10, 11). With Sulzbach she reported (11) the effect of mescaline on the EEG of normal subjects and was struck by the similarity between the choppy rhythm produced by mescaline and the one observed in a number of schizophrenic patients. This rhythm occurred simultaneously with the hallucinatory and catatonic symptomatology induced by mescaline. The observations of Davis (11) are concordant with those of Chweitzer and coworkers (5) and of Walter (48). However interesting these similarities are, it is difficult to explain the correlation between the EEG changes induced by the hallucinogenic drugs and the psychotic-like symptomatology. In addition to diffuse cerebral electrographic modifications other effects of LSD on individual neuronal systems have been studied. Evarts and Marchall (16) have examined the effect of LSD on the post-synaptic potentials in the lateral geniculate body evoked by single shock stimulation of the optic nerve and found that the transmission in the geniculate was markedly depressed by LSD while the cortical response to stimulation of the optic radiation was not inhibited. Marrazzi (30) reported that both LSD and mescaline

depress the response of the optic cortex to transcallosal stimulation. This depression is attributed to synaptic inhibition which assigns the hallucinogenic drugs to the group of synaptic inhibitors. The central synaptic effects of LSD at varying doses on different neuronal systems have been studied by Purpura (36). He found first of all an initial facilitation with small amounts of LSD, followed by depression with larger ones. The dose levels for these effects varied with the type of synapse studied. For instance the facilitation was most prominent even with relatively large doses for the primary potential of the visual area, while cortical response to stimulation of cortico-cortical and transcallosal systems was inhibited at relatively low dose levels. The differences noted by Purpura between the effects of small and large doses of LSD can be correlated with our observations showing that the general pattern of cerebral electrographic activity was desynchronized with small doses of LSD while large doses of the same drug reverse this effect. At this point it is worth mentioning that very large doses of LSD do not produce an excited behavior in monkeys as small ones do, but instead produce sedation (45).

Purpura (36) reported that the recruiting cortical responses from stimulation of midline unspecific thalamic nuclei, after an initial facilitation, are inhibited by LSD. We know that the electrographic alerting and the recruiting responses are competitive, for it is impossible or difficult to evoke recruitment while an alerting effect is taking place (25). This competition is probably due to the fact that recruiting and alerting responses are mediated through the same diffuse thalamocortical system. For this reason one wonders whether the long lasting alert electrographic pattern produced by LSD could be responsible for the apparent inhibition of the recruiting responses.

We have observed that Frenquel can correct the electrographic changes evoked by LSD and by mescaline. This fact, together with the observations of Fabing (17) that Frenquel cures the psychotic manifestations following LSD administration, seems to indicate an apparent antagonism between the central action of the hallucinogenic drugs and Frenquel. Moreover there is some kind of specificity because Frenquel corrects the electrographic alertness induced by the hallucinogenic drugs but not by DFP, amphetamine or Meratran. Very puzzling is the lack of antagonism observed in our studies between Frenquel and Meratran because Frenquel is chemically related to Meratran, the first being alpha 1-piperidyl benzhydrol hydrochloride and the latter being alpha-2-piperidyl benzhydrol hydrochloride. The results of Brown and coworkers (4) showing that Frenquel can tranquilize animals rendered over-excited by Meratran cannot be explained by antagonistic effects on the MDAS.

In view of the fact that the administration of hallucinogenic drugs renders the MDAS functionally overactive, one would expect that the antagonizing action of Frenquel should be due to a depression of the same system. We observed (40), however, that Frenquel administered alone is not at all a depressant of that system. For this reason Frenquel does not correct conditions of lasting alertness produced by the other drugs.

While the action of Frenquel seems specific in antagonizing the hallucinogenic drug effects, other drugs, like atropine, barbiturates and probably Chlorpromazine, act non-specifically. These three drugs are depressants of the MDAS and correct an electrographic alertness no matter how produced, whether by the hallucinogenic agents or by any other means. This explains, for instance, the results of Gastaut and coworkers (22) who observed that the administration of thiopental could correct the electrographic LSD-induced changes. Since thiopental is a short-acting barbiturate these authors could also observe the reappearance of the LSD effect after that of thiopental had vanished.

A suggestion for the mechanism of action of Frenquel in correcting the electrographic effects of hallucinogens can be sought in recent pharmacological data on the mode of action of LSD. It was found by Gaddum and Hameed (21) that LSD antagonizes the action of serotonin on the rat uterus. This antagonism is of the type usually described as receptor blockade: LSD combines with the receptors of serotonin thereby blocking their reaction with serotonin. In our laboratory Costa (7) has

studied the effect of several drugs on the serotonin-induced contractions of the rat's uterus. He confirmed the observations of Gaddum and Hameed (21) that LSD inhibits serotonin, but he also demonstrated that LSD, in concentrations lower than the inhibiting ones, facilitates the action of serotonin. Costa (7) also found that mescaline, in pharmacologically significant concentrations, always augments the serotonin-induced uterine contractions, while Frenquel, as well as the other tranquilizing drugs Reserpine and Chlorpromazine, inhibits serotonin.

On the basis of these findings we may attribute the electrographic alerting effect of mescaline and of small doses of LSD to a serotonin-facilitating mechanism. An inhibition of serotonin can be held responsible for the ability of Frenquel and of large doses of LSD to correct the electrographic changes. This interpretation is entirely hypothetical because the importance of serotonin in the function of the central nervous system is yet undetermined. Proceeding on the assumption that serotonin plays a part in brain physiology (49), our suggestions lead to the working hypothesis that the psychotogenic effect of mescaline and LSD is due to serotonin-facilitating properties. The correction of LSD-induced psychosis by Frenquel and probably the beneficial effects of Frenquel, Reserpine and Chlorpromazine in clinical psychiatry could be partially due to their ability to inhibit serotonin.

## Summary and Conclusions

1. A cerebral electrographic change, consisting in a long lasting alerting effect, follows the injection into rabbits of LSD in small amounts (1–15 gamma/kg.) and of mescaline. These findings correlate with EEG observations in psychotic patients and in volunteers under the action of LSD and mescaline.

2. Frenquel, which corrects the LSD-induced experimental psychoses, also eliminates the electrographic changes evoked by LSD and mescaline.

3. LSD in large amounts (20–60 gamma/kg.) has an effect on the cerebral electrical activity opposite to the one produced by small doses (1–15 gamma/kg.). This is correlated with the observation that LSD in very large quantities has a tranquilizing action.

4. These observations are tentatively explained on the basis of our pharmacological data and those of others. The production of electrographic alertness by the hallucinogenic drugs and their psychotogenic effect are attributed to a serotonin-facilitating property. The correction of the electrographic LSD- or mescaline-induced abnormalities by the use of Frenquel is attributed to the serotonin-inhibiting properties of that drug.

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# RHINENCEPHALIC ACTIVITY DURING THOUGHT[1,2]

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Chronic implantation of cortical and subcortical electrodes in human patients has provided a unique opportunity to explore the possible relations between the electrical activity in these regions and the subjects' verbalizations and behavior during psychiatric interviews. Attempts were made to correlate some types of reproducible electrical activity in specific areas with patterns of thought activity in selected patients.

This report concerns findings from four patients selected because they were relatively cooperative reporters during interview. Three were chronic schizophrenics. The fourth was being treated for intractable pain. Each had been evaluated by psychiatric studies and psychological testing which, with medical and social history, provided a broad background of information.

Recording electrodes were 1 mm. silver ball contacts implanted by use of stereotaxic coordinates implemented by air ventriculography. The electrodes and stereotaxic implantation method have been described in detail elsewhere (4).

Electrical recordings were obtained from at least five sites in each of the three psychotic patients. These included the region of the amygdala, caudate nucleus, rostral hippocampus, anterior hypothalamus, septal area, tegmentum of the mesencephalon, and frontal and parietal cortex. In the other patient, the only areas which could be examined were the anterior hypothalamus, septal region, and cortex. Corticograms and subcorticograms were recorded by a standard 8-channel Grass electroencephalograph.

Concurrent with electrical recordings, these subjects were interviewed repeatedly over a period of from six months to one year. Interview data were recorded directly on the moving EEG record by shorthand notes or, occasionally, on dual channel FM tape equipment which provided a simultaneous record of both electrical activity and interview. Interviews were directed toward both topics which were expected to be unimportant to the individual and to topics thought to be of special emotional significance in view of his life history. If a distinct change in electrical activity was elicited, attempts were made to shift the topic of discussion but to return to it later in the interview. In addition, electrical recordings were carefully observed for spontaneous changes during periods when the subjects were not being interviewed. If a change in electrical recordings occurred, the subjects were immediately questioned concerning their thoughts and feelings.

Various modalities of peripheral stimulation (e.g., touch, sound, light, odor, etc.) were tested for their effect in evoking changes in electrical recordings.

## RESULTS

A distinct, reproducible change in the pattern of electrical activity was observed which correlated with data obtained during interviews. This change was localized to the rostral hippocampal and amygdaloid areas. Baseline records from this region show a mixture of slow and fast frequencies and appear irregular and "desynchronized". The change in pattern consisted of distinct bursts of 14–17/sec. waves from rostral hippocampus and 20–30/sec. waves from the amygdala together with an increase in amplitude which gave the appearance of more synchronous activity. The duration of the change varied from several seconds to 20 minutes. In no case did this change in pattern of electrical activity spread to other subcortical areas examined or include the cerebral cortex.

The electrical response was immediate and dramatic. It could be elicited repeatedly or promptly terminated by appropriate direction of the interview. This is illustrated in figure 1.

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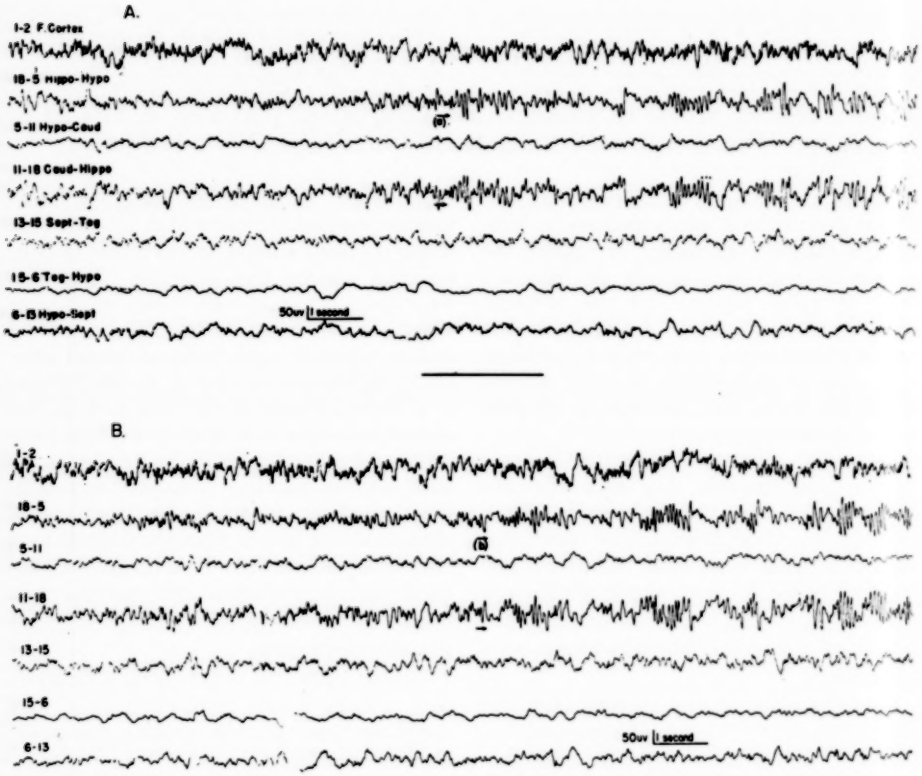


FIG. 1. Above: (Patient A-10) Illustrated in the record (A) is an immediate change in recordings (from channels 2 and 4, reflecting hippocampal electrode 18 activity) as the subject began to recall a vivid childhood memory at the point marked by arrow (a).

Below: Record (B) shows a sample of recordings later in the same interview. Recordings returned to baseline level when the interview was directed toward current symptoms. Baseline activity on the left persisted until he began to recall an important past experience at point marked by arrow (b). Further description is given in the text.

In the record "A" is seen an immediate change in hippocampal activity as the subject began to recall his grandmother who was a significant and feared individual during his childhood. At the point marked by arrow (a) he reports, "A thought comes to mind of my grandmother's face—her teeth stuck out—like a witch!" The record returned to baseline level when the interview was directed toward current symptoms. Baseline activity persisted as he complained of inability to express emotion, loss of interest in his surroundings, and loss of appetite. He was then asked if he could recall a time when he felt differently. High voltage 14/sec. hippocampal activity reappeared immediately at arrow (b) as he recalled an episode associated with a rare sense of well being and success. The change continued as he reported, "I felt good and was happy—then even the cold army stew tasted better than turkey and steak do now!" Figure 2 illustrates a typical baseline record during an interview with the same patient one month later. On the right hippocampal, recordings again changed markedly as he described stressful events and his anger toward military authorities which immediately preceded his first overt psychotic episode 12 years ago.

This characteristic type of electrical activity was usually associated with vivid recollections of past experiences by the subjects. These memories were judged to be of special emotional significance in view of the life history of the individual. The emotional quality

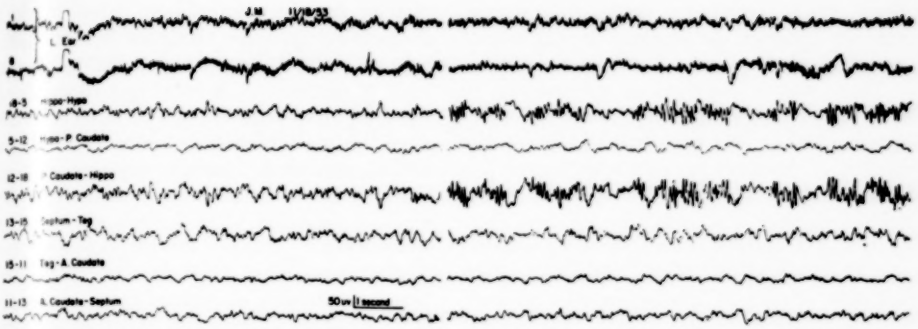

FIG. 2. Same subject interviewed one month later. On the left is typical baseline record. On the right hippocampal activity (reflected in channels 3 and 5) again changes markedly as he describes stressful events immediately preceding his first overt psychotic episode.

of these reminiscences was not specific, and they could be designated as either pleasant or unpleasant ones. The degree of accompanying emotional expression was variable and did not seem directly related to the electrical response. These memories were only rarely accompanied by any overt manifestation of intense emotion such as agitation, tachycardia, or gross changes in vasomotor or sudomotor activity. Unfortunately, precise studies reflecting peripheral autonomic activity were not included.

The impression that intense emotional expression itself was not related to the electrical change is further illustrated by the following two examples: 1) In the same subject this localized recording change was not seen during marked expression of anger appropriately directed and concerned with a recent episode on the ward. Baseline activity persisted as he cursed ward personnel because they failed to submit a consultation. In this same subject changes in electrical activity could be induced easily and repeatedly by directing the interview to a variety of important past experiences including those involving anger as was illustrated in figure 2. 2) In another patient administration of lysergic acid induced a state of panic for a period of six hours during which her thinking was disorganized, she was markedly agitated, and had tachycardia of 130/min. She complained of intense fear, but was unable to account for her feelings or relate the fear to past experience; despite this, the electrical recordings failed to show the characteristic changes. The same individual did show 16/sec. hippocampal activity on other occasions when fear was induced by recollection of EST therapy. On these occasions similar agitation, tachycardia, hyperpnea, and sweating occurred; but she was able to associate her feelings of fear with past experiences with EST.

There was also no characteristic change in electrical activity during thoughts involving current events, present symptoms, and recent family or ward difficulties. Nor was there a change in electrical recordings when the subject solved arithmetic problems or performed routine tests of retention and recall. This proved to be one convenient way of distracting the subject's attention from emotionally charged memories and returning records to baseline activity after changes had been elicited.

Occasionally the same localized change in electrical recordings would be seen when the subject was not being interviewed. Immediate questioning often revealed that spontaneous thoughts had been concerned with emotionally significant past experiences.

Of the various modalities of peripheral stimulation applied, olfactory stimuli proved to be unique in eliciting a similar localized electrical response. The same pattern of response could be evoked when it was suggested that the subject think of an odor or "smell" an empty bottle. Synchronized bursts of longer duration occasionally resulted when the odor was associated with significant memories in two patients. Olfactory stimuli or thoughts of

odors could result in electrical response, whether regarded as pleasant or unpleasant by the subject.

There was a variation in accessibility to interview, in the distinctness of electrical response, and in the ease with which it was elicited in the three patients who showed this response. One patient (A-10) who was an excellent reporter and clinically the best integrated of the three schizophrenics presented the most consistent findings. He is a 31-year-old male of superior intelligence who has been unable to maintain any steady employment since his first overtly psychotic paranoid reaction 12 years ago. At that time while under stress of war combat, he developed hallucinations, persecutory and somatic delusions, felt he was being directed by a vague force, and began to experience sexual fantasies which he terms "incest fantasies". Subsequent to this he was hospitalized on four different occasions and treated with several courses of EST and deep insulin comas with only partial and temporary improvement. Prior to the present admission he received four years of psychotherapy with little benefit. On present admission, his symptoms included chronic somatic delusions, ideas of reference, feelings of unreality and depersonalization, and a sense of hopeless apathy and impending doom. His chief complaints included persistence of "incest fantasies" and an inability to experience emotion. He expressed this as "an emptiness—life has lost all its glitter and glamour—I have an idea of what it is to have emotions, but I just can't feel anything—my feelings are just poof—everything around me has a grey, dull look to it." Among the patients in this study, he was outstanding in his ability to verbalize his thoughts, feelings, and fantasies. He described fantasies and past events in his life with unusual vividness. He spoke of some of his memories as being "as clear as if I were re-living them." It was possible to alter his hippocampal recordings repeatedly over a period of many months (see figures 1 and 2). This was accomplished by directing the interview to a variety of topics found to be important in his past history, by having him associate to specific words, or by suggestion that he recall important experiences or individuals from his past. The record returned to baseline activity immediately when he was distracted from these thoughts (for example, by an arithmetic problem or a change in the topic of discussion). Spontaneous thoughts of significant past experiences were often reported when he was questioned immediately after similar recording changes occurred during times when he was not being interviewed. The reported thoughts which correlated with the characteristic change in hippocampal recordings concerned vivid memories of emotional significance as judged from his longitudinal history. They could be either pleasant or unpleasant. These memories were never accompanied by any gross signs of intense emotion.

In addition to the reminiscences mentioned under figures 1 and 2, there were many other types of thoughts and memories which would consistently evoke the same change in hippocampal activity. Among other examples are 1) recalling the melody of the song "Lili Marlene" which he associated with a specific period of military duty during which he felt depressed; 2) an attempted solicitation by a homosexual years ago which frightened him; 3) the smell of alcohol which recalled the breweries in his home town as a child and a later period of alcoholism.

In another patient (A-16), who reported her thoughts very incompletely, bursts of 20–26/sec. waves from the amygdaloid region and 15–17/sec. from the rostral hippocampal region were elicited less frequently and less consistently. She is a 34-year-old former social worker who had responded with decreasing improvement to a number of courses of EST during hospitalizations over the past eight years. She usually appeared disheveled, with pockets bulging with an assortment of debris collected on the closed ward. She was cooperative but often confused and distractible. Her effect was flat with inappropriate silly grinning.

One vivid childhood memory with an olfactory component would almost invariably be accompanied by a characteristic change in recording. This is illustrated in the upper record of figure 3: bursts of 26/sec. waves from the amygdaloid region and less distinct 16/sec. waves from the hippocampal region. This activity was elicited at the point marked by

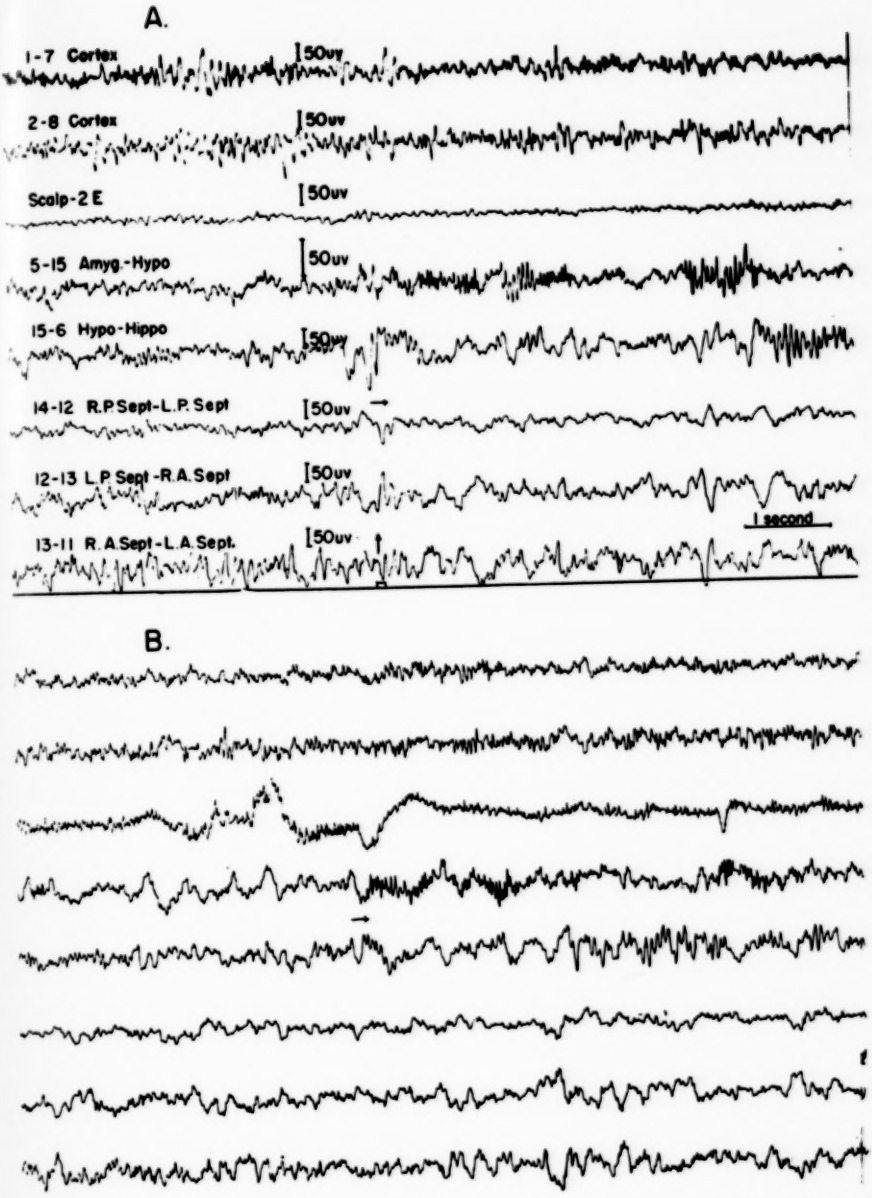


FIG. 3. (Patient A-16) Record A: Bursts of 26/sec. activity from the amygdaloid region (channel 4) and less distinct 16/sec. waves from the hippocampal region (channel 5). This activity was elicited at the arrow mark when the patient recalled a specific emotionally significant memory. The same memory was repeatedly accompanied by a similar electrical change.

Record B: A similar change in activity is seen. This response was elicited by an olfactory stimulus indicated by the arrow. (Electrode positions same as above.)

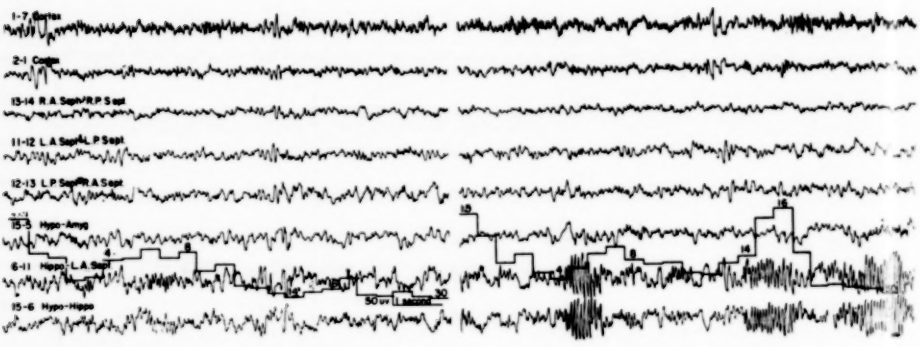


FIG. 4. (Patient A-16) On the right is an example of bursts of high amplitude 16/sec. activity which appeared while the patient was agitated and reported fearful thoughts about electric shock therapy. In contrast, on the left is a section of the recording while she was speaking of a less emotionally charged topic. Superimposed is frequency analysis histiogram of channel 7 demonstrating marked increase in the 16/sec. band.

the arrow when the patient was asked to recall a retired school teacher who for several years cared for her and served as her private tutor. The elderly teacher was known as an "eccentric" individual who kept a locked room filled with an assortment of mementos, old newspapers and even pieces of dried fruit. Thoughts about the teacher or of the odor which the patient identified with her room were repeatedly accompanied by a similar electrical change. A similar change seen in the lower record of figure 3 was elicited by an olfactory stimulus indicated by the arrow. Less consistently, localized subcortical changes would accompany other thoughts when she appeared clinically less preoccupied; for example, while she associated the odor of gardenias with a school dance, or while she first displayed interest in the examiner and reported that he made her "feel unrejected" and reminded her of her former boy friend. This was the patient mentioned previously who on several occasions reacted with marked agitation when describing her fear of EST (see figure 4).

The third patient is a 28-year-old former janitor, with a long history of seclusiveness, who was known to have been actively hallucinating for at least four years. He was a cooperative, quiet individual with flattened affect, stereotyped thought processes, and autistic preoccupation. Clinically, he was the least accessible of the group. He demonstrated changes localized to the amygdaloid area (30/sec.) only in response to olfactory stimuli, or occasionally to the thought of odors. Recordings at times when he was actively hallucinating "the voice of God" showed no change in electrical activity.

In a fourth patient without hippocampal or amygdaloid electrodes, no consistent changes could be induced in electrical recordings from the cortex, anterior hypothalamus, or septal region to either interview or odor. She was a good reporter and frequently reacted with marked emotional expression during interviews. This patient was under treatment for control of intractable pain and had no psychiatric diagnosis.

## DISCUSSION

These few patients have provided us with a unique opportunity for an exploratory study which has yielded several interesting fragments of information. A number of practical limitations must be taken into account, however, in the interpretation of the data obtained. The precise anatomical localization so easily obtained by sacrifice and histological verification in animal experimentation is impossible, and reliance must be placed on the less exact method of stereotaxic implantation aided by ventriculography. The subjects studied were schizophrenics who are clinically described as exhibiting impairment of thought processes and affectivity, and the effect, if any, that this may have upon our findings is not known. In addition, our concept of what con-

stitutes "emotion" is unclear. An obvious difficulty has been in the definition of emotion as applied to the thoughts and memories the subjects reported. More precise and systematic experimental analysis in this direction is feasible and will help to clarify the meaning of these observations.

These studies demonstrated distinct, reproducible changes in the electrical activity of certain subcortical areas that were evoked or terminated repeatedly by directed interviews. The change in electrical recordings was localized to the amygdaloid and rostral hippocampal regions. This pattern of activity did not spread to other subcortical regions examined, nor was it reflected in cortical recordings. These localized, high voltage, regular wave trains were found to be correlated with thoughts expressed during directed interviews and also occurring spontaneously. This electrical pattern appeared to be associated with emotionally significant memories as defined in terms of the life history of the individual.

This type of rhinencephalic activity did not appear to be correlated with the expression of emotion. The vivid recollections of past experiences associated with the characteristic electrical activity were most often without any behavior or peripheral signs suggestive of marked emotional expression. Gross agitation, tachycardia, etc., did occur on rare occasions during such recollections. Expressions of anger directly connected with a recent ward episode were without effect in changing the record. Nor was the characteristic electrical change evoked by drug (lysergic acid) induced states of panic when the individual's thinking was disorganized and she was unable to account for her fear, or associate it with her past experience. In addition, the electrical change was not associated with states of attention and alertness such as those required to solve mathematical problems. The mere process of recalling thoughts without special emotional significance to the individual (such as that involved in routine retention and recall tests) was never effective in eliciting this electrical response.

This change in electrical activity was found in rhinencephalic structures which have been suspected of important neural influence on a wide variety of phenomena from olfaction to psychomotor epilepsy. The observation that changes in the activity of the rostral hippocampal and amygdaloid regions could be induced in our subjects by olfactory stimuli and frequently by thoughts of odors or memories associated with them is interesting. The demonstration that similar electrical activity is elicited in this area by both emotionally significant memories and odors is interesting in view of the history of theories concerning the functions of these structures. The old presumption that all the structures comprising the rhinencephalon primarily serve an olfactory function is no longer accepted. Conjectures connecting sense of smell with emotional states and memory are even more venerable; for example, an observation quoted by Darwin, "The sense of smell in man is singularly effective in recalling vividly the ideas and images of forgotten scenes and places." (1, pp. 405–406).

These electrical changes were demonstrated in rhinencephalic areas currently suspected of having a regulatory influence on emotion, visceral reactions, and memory (6, 8, 9).

Studies of induced changes in the electrical activity of this area in unanesthetized animals are of special interest. Several workers have reported that a variety of afferent stimuli could evoke distinct changes in activity in the hippocampus (2, 5, 7). In a recent publication (3) Green and Arduini reported a study of high amplitude hippocampal wave trains with "aroused" cortical recordings that could be easily induced by a wide variety of afferent stimuli such as touch, click, etc. In addition, these included some stimulus situations presumably more meaningful to the rabbit, e.g., sexual excitement, the odor of carrots, the sight of a predatory animal, and in general "threatening situations". The hippocampal response was interpreted as a "specialized paleocortical arousal reaction". It was noted that these changes in hippocampal activity were induced easily in the rabbit, but evoked with much more difficulty in cats, and still more difficulty in the monkey.

The caution required in making comparisons and extension of the interpretations of animal experiments to man is also required in the reverse situation. The electrical activity we observed may in certain respects be analogous to the induced synchronous activity in the

rabbit. If comparisons can be made, it would appear that the hippocampal response in the human is induced by more limited but at the same time more complex stimulus situations than those necessary in the rabbit. The electrical response we observed was elicited during recollections of past experiences which appeared vivid and of emotional significance to the individual subject in terms of his life history. Simple afferent stimuli (except odors), attention and alertness while performing intellectual tasks, expressions of emotion without recall of past experiences, and states of panic when thinking was disorganized were all inadequate in evoking this response.

One characteristic aspect of human behavior is man's ability to use speech to communicate his thoughts and feelings. This type of communication by our subjects has provided some information concerning the occurrence of a distinct type of physiological activity in certain subcortical regions.

## Summary

Patients with chronically implanted cortical and subcortical electrodes provided an opportunity for an exploratory study of the electrical activity of these areas during interview. These studies demonstrate distinct, reproducible changes in electrical recordings localized to the amygdaloid and rostral hippocampal regions. These changes were correlated with both thought activity elicited during directed interviews and occurring spontaneously. It was suggested that this type of rhinencephalic activity is related to emotionally significant memories. Similar electrical responses were elicited by olfactory stimuli and thoughts related to odors.

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# CHEMICAL CONSTITUENTS OF HUMAN BRAIN[1, 4]

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Systematic quantitative studies on the constituents of various structures in human brain are difficult to find in the literature. The largest collection is that reported by Randall (13) on parts from 23 adult brains. A biochemical mapping of the brain during development and in maturity should give us added information as to the function of various parts of the brain and the biochemical mechanism involved in those functions. The data presented here are, in effect, a preliminary report of a long term study devoted to such biochemical mapping. The brains analyzed were from individuals who died from a variety of causes and who had been dead a variable number of hours before autopsy. In such individuals we must also consider the possibility that areas of the brain were dead or dying before the person was declared dead. However, by analyzing only for those constituents known to change comparatively little after death we feel that valuable data may be obtained. We do not have enough observations as yet to attempt to correlate the range of values observed in constituents with the age of the individual, with the mental disease or with the causes of death. However, it is hoped that with a large enough series many of the observed differences will be explainable on these bases.

## METHOD

Brains of adult human beings, suffering from mental disorders but dying of natural causes, were obtained at autopsy, and samples of 25 to 40 anatomical areas from each brain taken for analyses. The patients were 61–87 years of age and of both sexes. Fetal brains, 26 to 40 weeks of gestation, and brains of infants dying in the neonatorum were either frozen and sampled after thawing or placed in a cold thermos jug and rushed to the laboratory. In either case the analyses were done immediately after thawing or after receipt. These brains will be referred to as immature brains.

Water and total nitrogen were determined on the same sample for adult brain. The tissues were dried at 95°C. under a vacuum of 30 inches of mercury to constant weight and transferred quantitatively to macro-Kjeldahl flasks for determination of total nitrogen by the usual Kjeldahl procedure. Separate samples for water and for nitrogen were taken from immature brains. Brain parts for L-glutamic acid were frozen in ether and dry ice, and wrapped in aluminum foil and freezer paper before being stored at −18°C. until analyzed. Parts for cholinesterase were treated similarly except that they were not frozen in dry ice and ether before storage. Cholinesterase was determined by the titrimetric technique described by Aprison, Nathan, and Himwich (2). The uniform procedure of freezing the brain parts for studies of cholinesterase was undertaken only after a statistical analysis of data obtained with and without freezing. The differences between the right and left caudates and colliculi of 12 rabbits whose brain parts were titrated as soon as possible after death were compared with differences obtained in a series of 12 rabbits when one caudate and one colliculus were analyzed immediately and the other caudate and colliculus frozen and then titrated. An analysis of variance showed $F = 13.53$ which is not significant, the 5% level being 249. The freezing procedure was therefore considered to have no significant effect on the cholinesterase of the brain under the conditions of our experiments. Free L-glutamic acid was analyzed microbiologically by the method of Sullivan and Strong (15). Specimens were taken by a neurologist who attempted to remove from each brain the same area of the structure being sampled.

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TABLE 1.—Cholinesterase of Adult and Fetal Brain Parts in mEq. of Acetylcholine Hydrolyzed Per Mg Wet Tissue × $10^6$ Per Minute

| Brain Part | Immature, Age 26–40 Weeks' Gestation | | | Adult, Age 61–87 Years | | |
|---|---|---|---|---|---|---|
| | No. | | Ave. | No. | | Ave. |
| | Brain | Sample | | Brain | Sample | |
| Caudate | 8 | 8 | 13.1 (8–21)§ | 14 | 26 | 30.( (15–5 |
| Putamen | — | — | — | 9 | 15 | 22.( (10–5 |
| G. pallidus | — | — | — | 9 | 15 | 14.( (6–6 |
| Colliculi, sup. | 7 | 7 | 8.6 (6–12) | 15 | 19 | 5.( (3–1 |
| Colliculi, infer. | — | — | — | 9 | 9 | 5.( (2–8 |
| Thalamus | 15 | 15 | 6.2 (4–9) | 14 | 27 | 5.( (2–1 |
| Medulla | 11 | 11 | 4.9 (3–6) | 10 | 10 | 3.( (1–7 |
| Cerebellum* | 15 | 15 | 4.7 (1–9) | 15 | 22 | 7.( (4–1 |
| Cortex† | 20 | 20 | 3.1 (1–5) | 14 | 26 | 2.( (1–5 |
| Spinal cord‡ | — | — | — | 13 | 13 | 2.( (1–5 |

* Lateral lobes.
† All areas averaged.
‡ Cervical.
§ Range.

## Results and Discussion

The data on cholinesterase (ChE) show that brains between 26 and 40 weeks after conception have the adult complement of ChE in the colliculi, the medulla, the thalamus, and in cortical gray according to wet weight (table 1). The levels in the caudate nucleus and in the cerebellum, however, are low in comparison to those in the adult. On a dry weight basis, however, with the exception of the caudate, the values for immature brains are 2 to 4 times greater than the corresponding values for the adult. These higher results may reflect the absence of contaminating or diluting substances, for example, phospholipids in the immature brain. Johnson, McNabb, and Rossiter (9) have shown that the ratios of total phospholipid in adult brain to that in infant brain are 1.78:1 for gray matter and 3.36:1 for white matter. Brante (5) has also found that total lipids are lower in the cortex of the fetus (3 months to term) than in the adult (65–90 years) being 12.4–16% and 17.6–21.3% of dry weight, respectively. Similar data are available for white matter, 14.0–22.9% for fetal brain; 24.6–26.9% for adult. It is also possible that in the adult brain cholinesterase may actually be lower than in immature or young brain. Aprison and Himwich (3) have shown that in the developing rabbit brain the various cerebral structures pass through a maximum and then decline in cholinesterase content as growth proceeds. The values given by Ashby and coworkers (4) on a 70-year-old male and those collected by Feldberg (7) from the literature compare well with our figures. The relatively high values for this enzyme in the caudate of the young and the caudate and putamen of the adult suggest that cholinesterase has some special function in these areas. Even in the youngest fetus we have studied (26th week of gestation), the caudate nucleus was definitely higher than other parts of the brain. The preponderance of ChE in the caudate is also marked in the rabbit even at an early age (3) and in the basal ganglia of the dog (7). The data quoted by Feldberg (7) for acetylcholine in man also show the same pattern.

We do not as yet have enough observations in each age group to differentiate the level of cholinesterase at various ages either in the fetus or the adult. The caudate, globus pallidus and putamen in the adult show more differences between the right and left sides of the brains than do any other of the structures studied. The tendency for the left caudate nucleus to be higher than the right in some adult brains is an interesting subject for speculation.

The water content of thalamus and cortical gray from immature brains ranged between 90–91%. These high values are in contrast to the relatively dry state of adult brain. In the adult the spinal cord and medulla were the driest, while the lateral lobes of the cerebellum were highest in water content (table 2). Our data fall within the range described by Randall (13) but average slightly higher. The values approximate those of Johnson, McNabb and Rossiter (9) who reported 91% water for both white and gray matter from five infant brains and 84.2 and 73.5% for gray and white matter, respectively, from five adult brains and those of Brante (5) who found 84.9% water content in human cortical gray matter. The data of Tupikova and Gerard (16) on the dog and of Graves and Himwich (8) on the rabbit show the same tendency of the phyletically older parts of the brain to be lower in water content than the younger areas. In the adult brains we have studied, the various structures follow a neurophyletic progression except for the cerebellum. There are several lines of investigation suggesting that the lateral lobes of the cerebellum are close phyletic to the cortex since they develop together (12). Dixon and Meyer (6) have reported that the cerebellum of the ox has a higher oxygen consumption than does the caudate nucleus or the cerebral cortex.

Total nitrogen representing as it does largely protein and amino acid nitrogen, but also including phospholipids and other nitrogen containing substances in brain, would not be expected to change markedly in total amount after death although the distribution among the various nitrogenous substances might be altered. In the immature brains, on a wet weight basis, the medulla ranked highest followed by the cerebellum, the colliculi and the thalamus in that order (table 3). Cortical gray had the lowest nitrogen content. This series suggests a neurophyletic arrangement except for the high value exhibited by the cerebellum which, however, might be expected because of its late phyletic development to be closer to the cortex. It is possible that the cerebellar samples taken from the immature brains included the vermis. Kelley (10) has shown that both the vermis and the lateral lobes of the cerebellum in the rabbit have a higher nitrogen content (wet wt.) than the other brain parts as early as the fifth day after birth and that this relatively high level persists into adult life. The cortex and caudate gradually approach the high level of the cerebellar structure as the animal matures. We do not have data on the rabbit which would correspond to the age of the adult brains used for this study. In the case of the immature brains, we have as yet so few data on water content that it is useless to translate the nitrogen values to percentage of dry weight.

In the adult brain on a wet weight basis, total nitrogen is higher than in the immature organ. The medulla, inferior and superior

TABLE 2.—WATER CONTENT OF HUMAN BRAIN PARTS

| Brain Parts | No. | | Adult, 67–87 Years |
|---|---|---|---|
| | Brain | Sample | Ave. % |
| Cerebellum* | 10 | 11 | 83.8 (79–91)§ |
| Cortex† | 8 | 9 | 82.4 (79–86) |
| Caudate | 10 | 13 | 82.4 (80–86) |
| Putamen | 8 | 9 | 79.9 (70–88) |
| Thalamus | 10 | 11 | 78.5 (73–85) |
| Colliculi, superior | 10 | 10 | 78.5 (74–83) |
| Colliculi, inferior | 5 | 5 | 78.4 (78–81) |
| Medulla | 10 | 10 | 73.5 (69–77) |
| Spinal cord‡ | 8 | 8 | 71.6 (69–77) |

* Lateral lobes.
† All areas averaged.
‡ Cervical.
§ Range.

TABLE 3.—TOTAL NITROGEN OF HUMAN BRAIN PARTS IN PER CENT OF WET WEIGHT

| Brain Parts | No. | | Immature Brains, 26–40 Weeks' Gestation | No. | | Adult Brains, Age 61–87 Years |
|---|---|---|---|---|---|---|
| | Brain | Sample | | Brain | Sample | |
| Medulla | 12 | 23 | 1.50 (0.95–1.96)§ | 8 | 8 | 2.16 (1.70–3.20) |
| Cerebellum* | 14 | 26 | 1.34 (0.99–1.68) | 8 | 9 | 1.84 (1.52–2.29) |
| Thalamus | 13 | 26 | 1.21 (0.98–1.43) | 7 | 9 | 1.83 (1.54–2.09) |
| Colliculi | 7 | 12 | 1.30 (0.91–1.97) | — | — | — |
| Superior | — | — | — | 7 | 7 | 2.05 (1.68–3.01) |
| Inferior | — | — | — | 6 | 6 | 2.21 (1.60–2.44) |
| Putamen | — | — | — | 7 | 7 | 2.03 (1.46–2.68) |
| Caudate | 7 | 14 | 1.10 (0.80–1.26) | 8 | 12 | 1.83 (1.54–2.39) |
| Cortical gray† | 19 | 37 | 1.08 (0.84–1.37) | 8 | 35 | 1.59 (1.07–2.13) |
| Spinal cord‡ | — | — | — | 5 | 5 | 1.88 (1.69–1.96) |

* Lateral lobes.
† All areas averaged.
‡ Cervical.
§ Range.

colliculi, and the putamen showed approximately the same total nitrogen content (table 3). The lateral lobes of the cerebellum, thalamus and cervical spinal cord had figures very close together but less than the putamen. Cortical gray matter was still the lowest in terms of nitrogen content. This order bears little relation to a neurophyletic one. However, it would be surprising if, in the brain, after maturity, a truly phyletic arrangement could be described for such an ubiquitous constituent as nitrogen.

In the nitrogen data based on dry weight we included only those brains on which we had both water and nitrogen determinations. On this basis, the cervical spinal cord and medulla had definitely the lowest content of nitrogen. At the other end of the series were the lateral lobes of the cerebellum. The remaining structures analyzed fall fairly close together between the cerebellum and the medulla. The only similar values we have found in the literature are those of Randall (13). It is difficult to compare our data with his since he examined only three parts which were comparable to ours, namely the thalamus, and the frontal and the parietal cortex. For these structures our values were one to two per cent higher than his. This fact is probably a reflection of the higher water content we found in these structures. No obvious reason for these differences is apparent; they probably represent only the normal variability to be expected.

Of the three constituents studied we have been most concerned with an increase of free L-glutamic acid after death. However, since for 18 structures analyzed only two showed a difference of more than one mg.% in the free L-glutamic acid between the average values of brains removed 1–28 hours after death and those removed 1–78 hours after death, two brains removed at 48 and 78 hours postmortem have been included. It is possible that autolysis which could release L-glutamic acid from proteins proceeds explosively in the first few hours after death and then slackens or proceeds at a negligible rate if the body is refrigerated promptly. Ansell and Richter (1) have demonstrated an unstable "neutral proteinase" in rat brain which is active for only 1½ hours after death. If such a proteinase

TABLE 4.—FREE L-GLUTAMIC ACID IN HUMAN BRAIN PARTS IN MG. % FRESH TISSUE

| Brain Parts | Immature Brains, 26–40 Weeks' Gestation | | | Adult Brains, 61–87 Years | | |
|---|---|---|---|---|---|---|
| | No. | | mg. % | No. | | mg. % |
| | Brain | Sample | | Brain | Sample | |
| Medulla | 8 | 8 | 261 (169–355)§ | 13 | 13 | 251 (96–473) |
| Cerebellum† | 13 | 13 | 220 (136–298) | 19 | 19 | 295 (100–672) |
| Thalamus | 13 | 14 | 215 (142–298) | 21 | 21 | 284 (176–442) |
| Caudate | 8 | 8 | 172 (99–263) | 25 | 25 | 291 (187–493) |
| Cortical gray‡ | 5 | 6 | 142 (114–223) | 24 | 24 | 293 (159–438) |
| Globus pallidus | — | — | — | 13 | 13 | 345 (91–733) |
| Putamen | — | — | — | 14 | 14 | 377 (212–722) |
| Spinal cord* | — | — | — | 9 | 9 | 475 (86–988) |
| Colliculi, sup. | — | — | — | 11 | 11 | 256 (97–367) |

* Cervical.
† Lateral lobes.
‡ Frontal pole.
§ Range.

is present in human brain tissue, it is nearly impossible from a practical point of view to obtain normal values for free amino acids in human brain parts obtained post-mortem. On the other hand, brains removed at longer intervals after death may have shown no significant difference because the variations are so great as to mask changes due to autolysis in a series as small as this one. Certainly after five hours of the refrigeration to which the body is exposed the brain is cooled sufficiently to retard autolysis.

In the immature brain the cerebellum seems to have the highest complement of free glutamic acid. Next in order are thalamus, cortical gray, medulla, and caudate nucleus, all values falling fairly close together. In the adult, globus pallidus, putamen, and spinal cord are highest, and medulla is lowest in free L-glutamic acid. These values are on defatted as well as dehydrated tissue and therefore do not show differences which might be apparent in the fresh tissue.

When the glutamic acid values are converted to mg.% of fresh tissue, a different order appears. The frontal cortex is low at 142 mg.% (table 4), and the medulla is high with 261 mg. for the immature brains. The cerebellum from these brains again resembles the medulla as it did for total nitrogen, suggesting that vermis was included in these samples from immature brains. This arrangement is again suggestive of neurophylogenesis.

In the adult brain on a fresh tissue basis, there is more free glutamic acid than in the immature brains. The spinal cord had the highest value, with putamen and globus pallidus being considerably lower although still greater than the rest of the brain. The medulla and colliculi are lowest; the other brain parts slightly higher but they do not approach the values attained by putamen and globus pallidus.

These figures seem very high compared with those of 128–168 mg.% for brains of various other species (17). That these values are not due to some artifact in the microbiological method is suggested by a comparison of 120 mg.% for rabbit brain reported by Sullivan and Strong (15) and determined microbiologically with 152 mg.% by chemical analysis (17). The possibility still remains that the high

results may be due to autolysis. On the other hand, it may be a true species difference between rabbits and human beings.

In presenting the data we have combined the values from all areas of the cerebral cortex studied. However, throughout the analyses we have been conscious that there were differences between cortical gray matter taken from various parts of the adult brain. These differences, although not great, were considerably larger than expected in our laboratory between duplicate samples. The relation of one part of the cortex to another was not always constant, but there was a tendency for the occipital pole to be drier than either the frontal or temporal pole while, on a dry weight basis, total nitrogen tended to be higher in the frontal cortex than in the temporal or occipital poles. A typical analysis is shown in table 5. Such differences in areas of the cortex are not surprising considering the well-known differences in cytoarchitecture and electrical activity as well as the recently reported variations in blood flow (14). We have also found on those occasions when we sampled both the right and left sides of the brain that the samples often differed widely. This variation between right and left sides of the brain was not apparent in rabbits at least as far as total nitrogen content was concerned. Four rabbits at 84 days of age showed close agreement in total nitrogen of the right half of the brain of 1.70, 1.71, 1.70, and 1.70 per cent, respectively, and 1.74, 1.71, 1.72, and 1.75 per cent, respectively, on the left side (11). Cholinesterase in rabbits, on the other hand, showed more tendency to differ on the two sides especially in the caudate nucleus. The variation in this enzyme appeared to be no greater in man than in rabbits. These considerations suggest that those reporting chemical data on human brain should specify the anatomical location of the samples as well as the side of the brain.

TABLE 5.—J. M.—69 YEARS, SENILE PSYCHOSIS, CORONARY OCCLUSION, 4 HOURS DEAD

| | Water | Nitrogen (Dry Wt.) | Nitrogen (Wet Wt.) | L-Glutamic Acid |
|---|---|---|---|---|
| | % | % | % | mg. % |
| Frontal pole | | | | |
| Right | 90 | 16.10 | 1.61 | 234 |
| Left | 84 | — | — | 250 |
| Other frontal cortex | | | | |
| Right | 86 | 14.54 | 2.08 | — |
| Left | 83 | 12.48 | 2.11 | |
| Temporal pole | | | | |
| Right | 84 | 11.89 | 1.89 | 239 |
| Left | 83 | 9.76 | 1.66 | 177 |
| Occipital pole | | | | |
| Right | 82 | 10.27 | 1.90 | |
| Left | 80 | 5.46 | 1.07 | |

Our data, to date, suggest to us that the relative concentration of substances in the various parts of human brain may be more constant than the absolute amounts, that is, though the values differed, the structures ranked in the same order. For all the constituents examined greater variations in human brain were observed than in comparable studies on rabbit or rat. If one part of the adult human brain was higher than the average in a given constituent, e.g., N, all parts tended to be above the average for that same constituent.

## SUMMARY AND CONCLUSION

Areas from the brains of fetuses and babies dying in the neonatorum as well as from adult brains have been analyzed for water, cholinesterase, total nitrogen and free L-glutamic acid.

Cholinesterase activity is highest in the caudate both in the young and in the adult. In cortex, thalamus and superior colliculi, this enzyme appears to decrease with age.

In the immature brains, the distribution of total nitrogen and of free L-glutamic acid follows a neurophyletic pattern. In the adult brains this pattern is apparent only for water. Both nitrogen and L-glutamic acid increase in the adult brains on a fresh tissue basis.

Analyses of samples taken from different areas of the cortex suggest that each area has a unique chemical composition.

The relation of these findings to data available for other species is discussed.

We wish to thank Dr. M. H. Aprison for permission to use data on the cholinesterase content of five adult human brains and for the data on fresh caudate and colliculi from the right and left sides of rabbit brain.

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# SCHIZOPHRENIA—AN AUTONOMIC DISEASE[1,2]

A. HOFFER[3] AND H. OSMOND[4]

The development of hypotheses, although fraught with traps and difficulties, is a delightful scientific pastime. Whether the hypothesis is near or wide of the truth need not concern us as long as it is consistent and so formulated that it can be critically tested by the scientific method. We have developed such an hypothesis concerning the physiological mechanism of schizophrenia which has been most useful in developing our research program and in suggesting fruitful lines of investigation.

The hypothesis consists of the following five consecutive equations:

1. Biochemical constitution plus ??? → Autonomic change
2. Autonomic change (initial) = Increased parasympathetic activity
3. Autonomic change (secondary) = Increased sympathetic activity
4. Adrenalin detoxified (1) 1. via amine oxidase
   2. via sulfoesterase
   3. via phenolase

   Mechanism 3 predominates in schizophrenia with production of quinone indoles.
5. Quinone indoles interfere with cerebral metabolism.

A hypothesis has value if it unites a body of unrelated data into a satisfying relationship and if, in so doing, it stimulates the formulation of new research and thus the accumulation of additional data. If these equations have any value, they will allow us to draw certain subhypotheses or predictions from them. Common to all the equations is the conclusion that any factor which drives the reaction to the right will initiate and/or aggravate a schizophrenic process, and that any factor which slows the reactions to the right will decrease the intensity of the schizophrenic process and may be therapeutic.

Equation 1 is not a particularly good one but must be included as it sets the background for the other equations. Although it is certain that there is a very strong genetic basis for schizophrenia, no one has yet adequately described and reproduced those diverse unknown factors which set the process going. Autonomic disturbances are very frequently found in the schizophrenias, especially in the acute phases (9, 10).

Equation 2 is:

$$\text{acetylase} \xrightarrow{\text{A choline}} \text{esterase}$$

According to this equation, increasing the concentration of acetylcholine will aggravate or produce the schizophrenic process. Conversely its reduction will be therapeutic. We would, therefore, expect that the administration of compounds which tend to elevate acetylcholine levels will be harmful for the schizophrenic person. It has been shown that injections of acetylcholine into the ventricles of cats will produce a catatonic-like muscular reaction (6). Injections into the ventricles of schizophrenics produce the same reaction (21). If these injections are followed by acetylcholine esterase, the catatonic state is removed. Sherwood (27), in some very interesting research, has injected esterase into the ventricles of chronic catatonic schizophrenics. He prepared the patients by implanting a permanent interventricular cannula with the opening buried underneath the skin. With this arrangement it is possible to inject esterase periodically. He found a remarkable improvement in the clinical status of these chronic deteriorated patients although they were not cured. It is difficult to obtain pure esterase, and vegetative reactions were common.

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[2] Supported by the Department of National Health and Welfare, and Rockefeller Foundation Grants, Saskatchewan Committee on Schizophrenia Research.

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When patients are injected with atropine, prostigmine and acetylcholine (13, 28) in that order, they develop interesting reactions. Some schizophrenics developed a sleep EEG pattern without showing sleep activity subjectively. Other schizophrenics developed little sleeping activity on the EEG but showed a return of earlier florid symptoms. Thus this triad of drugs which produces sleep in normals and which elevates parasympathetic activity, the nicotinic phase, does aggravate in some cases the schizophrenic process.

If the concentration of acetylcholine is increased centrally, we might expect some spillover into the other body fluids, and this would necessitate in the blood at least increased concentration and activity of esterase to counteract the increased production of acetylcholine (23). It is interesting that Gellhorn found that the injections of schizophrenic serum into rats produced a parasympathetic type of reaction.

Acetylcholine esterase inhibitors will elevate acetylcholine concentrations, and if the above equation is reasonably good, these substances will produce schizophrenic-like reactions and aggravate those reactions already present. One of the best known inhibitors is physostigmine (11), which is an indole alkaloid. Physostigmine reversibly inhibits choline esterase and intensifies all the cholinergic activity of acetylcholine. It is perhaps impossible to find out what effect physostigmine has on the psychological structure when given in high quantities because of its toxic qualities. But it does increase the adrenalin content of blood, that is, the inhibition stimulates sympathetic ganglia. Another inhibitor is LSD (30), which recently has been shown to inhibit pseudocholine esterase of human serum. LSD (24), of course, is one of the most potent agents for the production of schizophrenic-like conditions. Another compound which is exceedingly active in this respect is bufotenine (26), an indole found in Piptadena peregrina, a plant which has been used as a euphoriant and intoxicant by North American Indians since the days of Columbus. Another inhibitor of acetylcholine esterase is adrenochrome (31), which has been shown to produce milder psychological changes of the same order as are found in schizophrenia (14). Intraventricular adrenochrome and adrenolutin produce trance-like states in cats. It thus appears that certain indoles are effective choline esterase inhibitors, and these indoles are now being recognized as active hallucinogenic agents.

Another group of compounds is the fluorophosphonates, for example, DFP. Both DFP and TEPP irreversibly inhibit esterase, the degree of inhibition depending upon the concentration. This substance, when administered for control of myasthenia gravis, produces insomnia, terrifying nightmares and hallucinations (7), and intraventricularly produces scratching and catatonia in cats (7). Rowntree, Nevin and Wilson (25) administered one to two mg. dosages daily to manic depressives, normals and schizophrenics. Marked changes were evidenced in normals and manic depressives, but little change was noted in schizophrenics. The first two groups became depressed during treatment, but nearly 50 per cent of the schizophrenic patients suffered reactivation of their original psychoses.

Other esterase inhibitors (12) include morphine, atropine, benzedrine, phenobarbital, caffeine. Anesthetics also inhibit (3) choline esterase. The delirium of the first and second stages of anesthesia can certainly be described as a psychological aberration.

Equation 3. According to this equation, the increased production of acetylcholine by stimulating sympathetic ganglia produces an increase in the secretion of nor adrenalin, some of which is methylated to adrenalin. It would, therefore, follow that increasing the rate of methylation of nor adrenalin to adrenalin will aggravate the schizophrenic process, whereas the inhibition or a decrease in the production of adrenalin will be therapeutic. It has been shown that the injection of 1 mg. of adrenalin sulfate subcutaneously (19) markedly aggravates the schizophrenic process in half the patients to whom it is given. The aggravation may last anywhere from a few minutes to several hours. Nor adrenalin forms a quinone indole with great difficulty, whereas this change occurs very readily with adrenalin. Noradrenalin, therefore, is not a toxic factor as far as schizophrenia is concerned, provided that it remains unchanged. It is even possible that if one were to block the methylation of nor adrenalin, one would achieve two objectives: 1) a decrease in the production of adrenalin and

therefore of adrenochrome and 2) a decrease in the production of nor adrenalin by a push-pull effect.

There are only four or five substances in the body which will accept methyl groups from methyl donors (2). One of these is nicotinamide; another is nor adrenalin. The methylation of nicotinamide results in the formation and the excretion in the urine of N-methyl nicotinamide (17). Nicotinic acid has some structural similarity to nor adrenalin. It is, therefore, conceivable that the introduction of large quantities of nicotinic acid or nicotinamide into the body will by competitive action decrease the methylation of nor adrenalin and, if this is true, nicotinic acid, and its amide will have some therapeutic action on schizophrenia. We have found that nicotinic acid (15) in dosages between 3 to 10 grams per day is a very useful treatment for most of the early schizophrenics and pseudoneurotic schizophrenias. We have now treated over 100 schizophrenic patients with nicotinic acid (15), with and without ECT, and have matched these results with patients who have received placebo treatment. Our results today show that of all the patients of the type admitted to the Munroe Wing (a psychiatric ward of a general hospital) with nicotinic acid 80 per cent remain well two years after discharge from hospital, whereas only one-third of all our patients receiving placebo remain in remission. Nicotinic acid has no therapeutic action on the great majority of very chronic schizophrenics. Both nicotinamide and nicotinic acid are equally effective for the treatment of early schizophrenia. Because nicotinic acid is a strong peripheral vasodilator, it has been suggested that any therapeutic action results from this cutaneous and therefore cerebral vascular effect. It has been clearly shown that niacin does not flush the brain (20) in the same way it flushes the face, and we have found that schizophrenics in a short time develop complete tolerance to the flush so that there is no longer a flush. The amide, of course, produces no flush, and as it is equally beneficial, this would rule out the vascular effect which has been postulated for nicotinic acid.

Equation 4. There is a very close direct relationship between the systolic blood pressure and the concentration of free adrenalin. Adrenalin is a very toxic substance, and if one postulates an increased production of adrenalin, one is forced to postulate an increased destruction. There may be a very slight increase in the adrenalin concentration in the blood, but it may be so slight that it cannot be measured. As I have outlined in the introduction, the adrenalin is detoxified by at least three definite mechanisms, only one of which results in the formation of quinone indoles. We suggest that the schizophrenic process is caused by some defect in the detoxification process of the normal mechanisms and thus an increased conversion of adrenalin into substances like adrenochrome or adrenolutin.

It follows, therefore, that medications which block the normal pathways of detoxication will produce or aggravate the schizophrenic process. Inhibitors of amine oxidase, when given in excess, will produce psychoses: for example, cocaine, methedrine, benzedrine, pervitin, lysergic acid diethylamide, morphine, caffeine, and atropine. Caffeine causes central excitation, insomnia, restlessness, and delirium, in large quantities.

According to this equation we would expect increased concentrations of quinone indoles in the body fluids even though the concentration of adrenalin is not elevated. Adrenochrome (18) and adrenolutin are antimitotic agents and inhibit mitosis in mouse epidermis. If, therefore, these compounds are present in blood, we would expect that schizophrenic blood serum would also have an antimitotic effect on mouse epidermal cultures. L-strain fibroblasts were originally obtained from a mouse epithelial tissue. We have found that over 90 per cent of all schizophrenics show a high toxicity for L-strain fibroblasts (5), whereas very few normals show any toxicity. We know that this toxic factor is heat labile. Schizophrenic blood which has four plus toxicity for L-strain cells shows no toxicity whatever for the Hela cell cultures obtained from human sarcoma. The toxic factor appears not to be a virus since the toxicity is directly related to the quantity of serum introduced into the medium and since, in a few cases, a few L-strain cells which have survived will recover and continue to grow in a normal manner. Recently, work on cerebrospinal fluids indicates that they are as toxic to the L-strain cells as are the sera.

We would also expect to find these indoles or some of their derivatives in the urine of schizophrenics. We have been examining schizophrenic urine for the presence of these indoles by means of paper chromatography and a special wool adsorption test. It appears certain that schizophrenic urine, especially that urine which is concentrated during the night, that is, the first morning specimen, contained much greater quantities of these indolic compounds than do normal urines. The substances appear to be of the type of 5-6 dioxy indole or melanin precursors (8) as they give specific tests for this type of compound.

We also would expect that quinone indoles derived from adrenalin should have properties we would expect a schizophrenic toxin to have. We have found that adrenochrome (14), when injected intravenously into human volunteers, and adrenolutin (29), when given orally to volunteers, produce marked psychological changes lasting anywhere from a few hours to several days. We have been able to produce perceptual disturbances, disorders of judgment, loss of affect, withdrawal of interest, severe depression, and other changes so commonly found in schizophrenia, with these compounds. We also have found that these compounds will aggravate the EEG abnormalities found in epileptic and some schizophrenic patients (29) and will produce marked EEG abnormalities in normal volunteers (16) who previously had none. Neurophysiologists believe that a disturbance in EEG pattern indicates an underlying disturbance in the production of energy. It thus appears that these compounds do somehow interfere with normal cerebral function. Finally, we have found that adrenochrome produces up to 80 per cent inhibition of rat brain tissue (32), whereas adrenolutin produces a marked acceleration of brain tissue respiration. Adrenochrome is perhaps one of the few substances which may be present in the body which has this marked inhibiting effect.

There are thus two basic conditions, according to our hypothesis, for the production of a schizophrenic process: 1) an increase in the concentration and activity of acetylcholine centrally and 2) an abnormal diversion of adrenalin into some quinone indole. We would, therefore, expect that any compound which will block acetylcholine esterase and which will cause an increased production of adrenalin, which is converted to an indole or which itself is an indole, meets these two conditions and ought to be a very powerful hallucinogenic agent. In table 1 are listed compounds which fulfill both these criteria (4). In the table, I have listed a few substances that inhibit choline esterase and which increase the production of adrenalin or are indoles. You will note that two substances, bufotenine and LSD, which are strong inhibitors and are indole themselves, are the most potent hallucinogens we know. Adrenochrome and adrenolutin are probably both strong inhibitors of esterase and, in addition, are quinone indoles quite probably present in the body. They are likely to be prototypes of the schizophrenic toxin. Substances such as serotonin, tryptamine, and caffeine stimulate the production of adrenalin as well as inhibit esterase. Serotonin is not hallucinogenic, but tryptamine produces catatonia (22). Caffeine is a euphoriant and in large quantities does produce toxic psychosis.

TABLE 1

| Hallucinogenic | Acetylcholine Esterase Inhibitors | Increase Production of Adrenalin or Are Indoles |
|---|---|---|
| strong | LSD (strong) | indole |
| strong | bufotenine (strong | indole |
| medium | adrenolutin (?) | indole |
| medium | adrenochrome (strong) | indole |
| mild | eserine (strong) | indole |
| mild | caffeine (mild) | stimulates |
| no | serotonin (mild) | stimulates |
| no | tryptamine (mild) | stimulates |

## Conclusion

This biochemical hypothesis has been our chief target for the past three years. We have not tried to work in any neuropathological theorizing due to our ignorance in this area. However, with this omission it has been a useful guide, and if it is not correct, at least it has been of value in summarizing a lot of data about schizophrenia.

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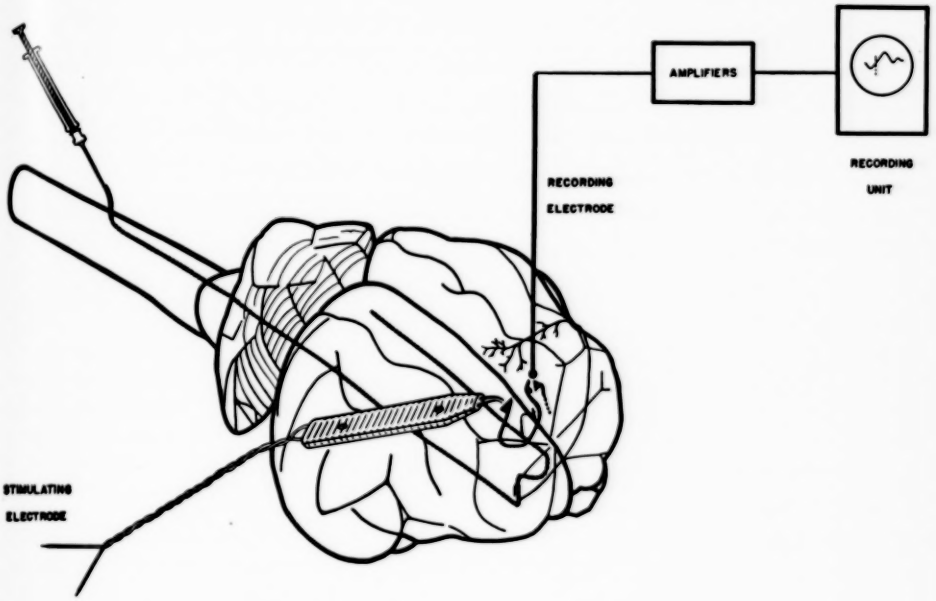
# THE POSSIBLE ROLE OF INHIBITION AT ADRENERGIC SYNAPSES IN THE MECHANISM OF HALLUCINOGENIC AND RELATED DRUG ACTIONS[1]

AMEDEO S. MARRAZZI, M.D., AND E. ROSS HART, PH.D.

The value of approximation and analogy followed by analysis is well known. The appeal and instructiveness of a model are equally familiar. Starting with an inclination in favor of an organic basis, we have attempted to utilize the animal and its neural circuits as a model in which to study the mechanism of psychoses and in particular those influences of drugs and endogenous chemicals which may have a bearing on the genesis and course of behavioral disorders in animals or mental disturbance in man. This kind of knowledge of this type of drug is required for the treatment of mental disease.




TRANSPARENT MODEL OF BRAIN

TWO NEURON INTERCORTICAL (TRANSCALLOSAL) PATHWAY

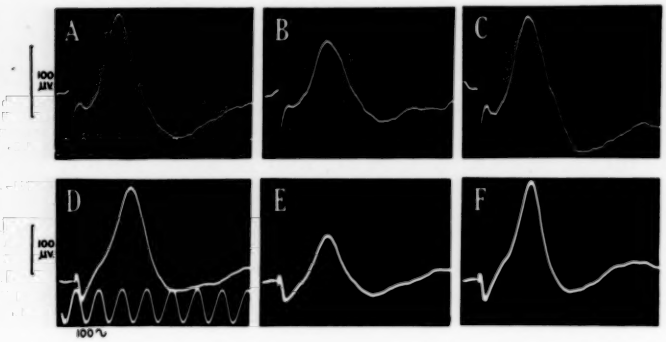
SCHEMATIC BLOOD SUPPLY (ARTERIAL)

PATHWAY FOR INJECTED MATERIAL

FIG. 1.

Since hallucinations with a visual component characterize many psychoses, we thought it pertinent to examine the influence of hallucinogenic and related substances on transmission phenomena in the visual system of the cat. In view of the higher vulnerability of the synapses in neural pathways we designed our experiments to test the susceptibility of

[1] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11-12, 1955.



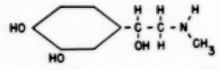

**CEREBRAL SYNAPTIC ACTION OF ADRENALINE AND OF NOR-ADRENALINE**

IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

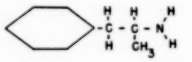
Potentials evoked in optic cortex by electrical stimulation of symmetrical point in contralateral cortex.
Adrenaline (10 μg./Kg.) injected ipsilateral carotid artery after A.
Nor-adrenaline (150 μg./Kg.) injected after D.

A, D - Controls B, E - Inhibition C, F - Recovery

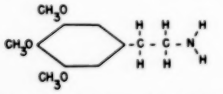
FIG. 2.



ADRENALINE (dihydroxy-phenyl-ethanol methyl amine)



AMPHETAMINE (phenyl-isopropyl amine)

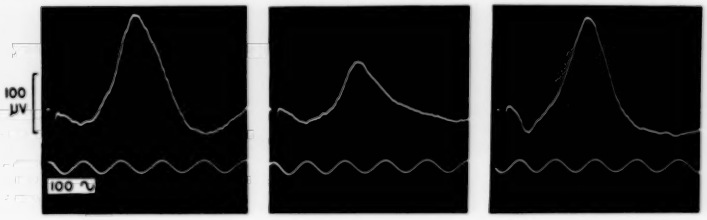


MESCALINE (trimethoxy-phenyl-ethyl amine)

**TYPES OF PHENYL-ETHYL AMINES PRODUCING MENTAL EFFECTS**

FIG. 3.

synapses to drugs. This was accomplished as illustrated in figure 1 by selecting a relatively simply pathway which connects symmetrical points in the optic cortices of the cat, initiating a test impulse by applying an electrical shock to one cortex and recording the electrical change produced by the nerve impulse arriving at the contralateral cortex immediately after having traversed one group of synapses. To achieve cerebral effects uncomplicated by actions upon the rest of the body, an initially higher concentration of drug in the cerebral hemisphere containing the synapses under study through action potential recording was achieved by injection into the common carotid artery of that side as illustrated in the transparent model (fig. 1). We had already had experience with the effects of adrenaline and noradrenaline in this preparation (1). The action potentials (as seen in fig. 2) show, following the stimulus artifact, a downward deflection or surface positive wave approximately corresponding to input to the synapse and an upward deflection or surface negative wave indicating arrival at the optic cortex, presumably following synaptic transmission. Following the control in the first column the intracarotid injection of 10 micrograms of adrenaline produces little or no effect on the portion of the curve corresponding to synaptic input but a considerable reduction of the surface negative wave. The third column indicates the recovery to the control level. This synaptic inhibition by adrenaline is reproduced in the next line by another neurohumor, noradrenaline, which takes, however, approximately 15 times the dose. Adrenaline, though




**CEREBRAL SYNAPTIC ACTION OF MESCALINE**
**IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM**

SPIKE POTENTIALS EVOKED IN OPTIC CORTEX OF THE CAT
BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS
MESCALINE HCl 15 MG./KG. INJECTION INTO FEMORAL VEIN

FIG. 4.

not a hallucinogen, does occasionally produce mental disturbance and supplies a lead because of its structural similarity (fig. 3) to amphetamine which produces mental disturbance somewhat more often, and mescaline which produces behavioral disorder in cats and mental disturbance with intense hallucinogenic effects regularly in man. We have therefore examined the effects of these substances also on the optic cortical preparation described, and they produce the same type of synaptic inhibition as that produced by adrenaline. The inhibition by mescaline is shown in figure 4.

Lysergic acid diethylamide (LSD-25) is an even more powerful disturber of mental processes than mescaline. In figure 5, its structure is compared to that of adrenaline and to its first oxidation product, adrenochrome, which is related to LSD-25 by the fact that like it, it contains the indole nucleus. Adrenochrome, in fact, has been claimed by Hoffer, Osmond and Smythies (2) to be capable of reproducing a schizophrenic-like syndrome in man when injected intravenously. LSD-25 through adrenochrome and adrenaline seems to be related to mescaline, and, therefore, it seemed of interest to determine the

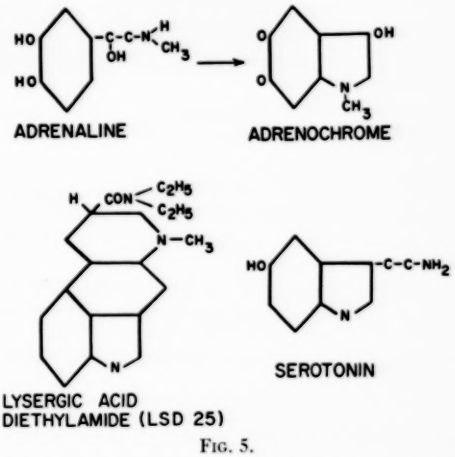
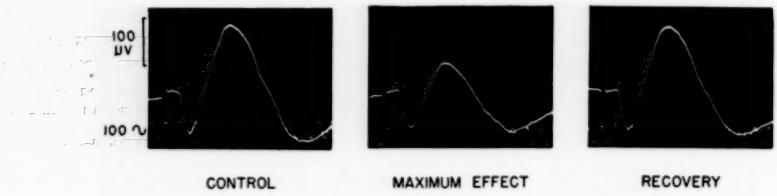



FIG. 5.

action of LSD-25 on the optic cortex. In keeping with the structural analogy drawn and the higher potency of LSD-25, it produces optic cortical inhibition (fig. 6) in a much smaller dose.

Serotonin or 5-hydroxy-tryptamine which (as seen in fig. 3) is another indole derivative having a close resemblance to adrenochrome has been suggested by Woolley and Shaw (3)




CEREBRAL SYNAPTIC ACTION OF L.S.D.25

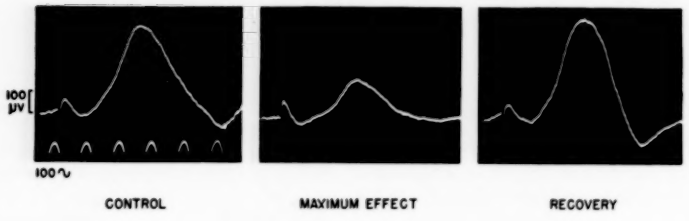
IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN OPTIC CORTEX OF THE CAT

BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS

L.S.D.25 8 μG./KG. INJECTED INTO CAROTID ARTERY

FIG. 6.




CEREBRAL SYNAPTIC ACTION OF SEROTONIN

IN A TWO NEURONE INTERCORTICAL (TRANSCALLOSAL) SYSTEM

POTENTIALS EVOKED IN OPTIC CORTEX OF THE CAT

BY ELECTRICAL STIMULATION OF CONTRALATERAL CORTEX EVERY 2 SECONDS

SEROTONIN 2 μG./KG. INJECTED INTO IPSILATERAL CAROTID ARTERY

FIG. 7.

as a possible competitive antagonist of LSD-25 because of the structural similarity with the latter as well. Trials on the same preparation reveal (fig. 7) that instead of antagonizing the synaptic inhibition, it produces the same type of inhibition and is considerably more potent in the cat than all of the other compounds mentioned. In fact, its effectiveness in gamma quantities qualifies this natural constituent of the brain for the role of a neurohumoral synaptic inhibitor. Instead of being an antidote for LSD-25, the findings suggest that serotonin or some related substance could well play the role of endogenous hallucinogen or cause of natural psychosis. Since we have previously demonstrated (1) in the synapses examined in this work and in a variety of other cerebral synapses that a balanced reciprocal relation exists between an adrenergic inhibitory mechanism and a cholinergic excitatory one, any factor tending to upset this balance could result in disturbance.

It seems plausible to postulate that cerebral synaptic inhibition plays a part in the action

of hallucinogens and other inducers of chemical psychoses of endogenous or exogenous origin, either by the direct disruption of normal patterns of synaptic activity responsible for behavior, or indirectly by inhibiting normal restraints and thereby releasing aberrant patterns of activity as a result of alteration in the normal balance between cholinergic excitation and adrenergic inhibition at susceptible cerebral synapses. A parallel hypothesis instead of placing emphasis on an excess of serotonin or a serotonin-like substance would place it on some other pathologic process creating an unusual sensitivity of certain synapses to such a normally-occurring substance. These considerations are basic to the development of effective and rational therapy of mental disease. It is evident that the search for therapeutic agents can at the same time quite effectively make use of drugs as tools in the analysis of the process which it is desirable to diagnose and to modify therapeutically.

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# CLINICAL, PSYCHOLOGICAL AND MYONEURAL CHANGES IN PSYCHOTIC PATIENTS UNDER ORAL SERPASIL MEDICATION[1, 2]

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The introduction of the new "tranquilizing drugs" (reserpine and chlorpromazine) has produced as much interest in psychiatric circles as did the introduction of insulin coma, metrazol and electro-shock treatment a score of years ago. The purpose of our experiment was to evaluate the effectiveness of Serpasil[1] by several methods: 1) clinical rating by medical and nursing personnel; 2) testing through usual psychological methods; and 3) probing for myoneural changes by the Mira Myokinetic Test. It is a known fact that clinical observation alone may at times be an unreliable judge of the effectiveness of a drug. With this in mind we attempted as many methods of measurement as possible. Since the beginning of this experiment others have engaged in similar research (4, 6).

## METHOD

Twenty-two physically healthy, male patients who were representative of the most disturbed patients were selected from the maximum security ward of Springfield State Hospital. These subjects were all schizophrenics; eight paranoid, ten catatonic, three simple and one hebephrenic. The average age was 38 years: fourteen being in the age group of 21 to 40; five, 41 to 50; and three, over 50 years old. Two patients had been hospitalized for less than 2 years; eight were hospitalized from 2 to 5 years; six, 5 to 10 years; and six were hospitalized for over 10 years. The average length of hospitalization was about 9 years, and the whole group represented 197 years of hospitalization. The estimated time of illness averaged 13½ years. Only two patients had been sick for less than 5 years, and twelve patients, for 10 years or more.

Previously 18 of these patients had one or more series of electro-shock treatments, and nine of these had a course of insulin coma treatment in addition to electro-shock. One patient had a transorbital lobotomy more than 4 years prior to the start of the experiment. It had been necessary to keep five patients almost constantly in seclusion. The subjects were divided into two groups of 11. Group no. 1 was given Serpasil orally for 12 weeks, followed by eight weeks of placebo. Group no. 2 was started on placebo which was given for eight weeks, followed by 12 weeks of oral Serpasil. The appearance of the placebo tablets was identical with the Serpasil tablets so that no one but the physician who dispensed the drug knew which patient received Serpasil. This physician did not participate in the evaluation of individual patients. All patients were given a routine physical and laboratory examination before the start of the experiment; the latter repeated at intervals. Weight and temperature were checked weekly, the pulse was checked three times a day, and blood pressure was taken once a day.

All patients were rated five times with the Multidimensional Scale for Rating Psychiatric Patients (M.S.R.P.P.) (7), three times during the Serpasil period and twice during the placebo period. An attempt was made to administer the Rorschach; Wechsler-Bellevue, Form I; Figure Drawing; and the Mira Myokinetic Test at the beginning and end of the experiment and at the point where medications were reversed. The patients were so disturbed and so uncooperative that complete psychological studies were not obtained. The Mira Test (2, 8) developed by Emilio Mira y Lopez has been widely used in South America and Europe though not in the United States. The test is properly called an expressive technique and proceeds on the premise that

[1] Reserpine (Serpasil) was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

[2] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

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emotional attitudes and personality are expressed in neutral space by muscular tensions and movement. The test consists of a series of designs to be drawn without sight with the dominant hand of the subject, then with the other hand. The designs are lines, zig-zags, stairs, parallels, etc., drawn in sagittal and vertical planes. There are 79 different measurements per test besides the qualitative evaluations. It must be clearly understood that the results obtained in this experiment are based on Mira's norms on a foreign population since the American norms are not yet complete. All tests were evaluated as to changes in anxiety, aggression, reality testing, and interpersonal relationships. The Mira was also used to determine changes in muscular tone.

## Dosage

Except for one patient who refused medication in the beginning and who was given intramuscular injections for one week, all Serpasil medication was given orally. Generally, the initial dosage was 0.5 mg. t.i.d. which was increased by 1 to 3 mg. daily unless the patient complained of side effects (namely, headache, extreme fatigue, salivation) or until he showed symptoms of Parkinsonism. In such cases the amount was reduced and continued on this new level until the end of the Serpasil period. The maximum dose given any patient was 15 mg. daily. The average of the highest dose given to Group no. 1 was lower (7.3 mg. daily) than in Group no. 2 (12.2 mg. daily).

## Controls

A matched control group was not used; however, each patient served as his own control during the eight weeks of placebo, before or after Serpasil medication. This type of control appeared efficient for this experiment. Since most of the patients had been hospitalized for many years, their behavior was well known to the ward personnel and the physicians. The patients were kept under identical conditions during the experiment and control period, and no other treatments were given except an occasional aspirin or bed rest for a cold. Those who were able continued to go to the gymnasium, work on the ward or in the occupational therapy shop. In effect nothing was changed in the lives of these patients except the addition of the experimental procedure.

TABLE 1

| | Average of Last Week of Placebo Treatment | Average of Last Week of Serpasil Treatment |
|---|---|---|
| Pulse rate | 86 | 74 |
| Systolic B.P. | 113 | 105 |
| Diastolic B.P. | 71 | 64 |
| Pulse pressure | 41 | 40 |
| Body weight | 151 | 155 |
| Body temperature | 99.0 | 99.2 |

## Results

In the beginning of the experiment it was thought that Serpasil was responsible for sudden drops in blood pressure and pulse rate. It was soon found that drops of systolic blood pressure to 80 and of pulse rate to 40 did occur spontaneously in schizophrenics under placebo as well as under Serpasil treatment. The average of blood pressure, pulse rate, temperature and body weight of the last placebo week was checked against that of the last Serpasil week (table 1). The average pulse rate was always slightly lower under Serpasil treatment. Systolic as well as diastolic blood pressure was generally, but not always, lower at the end of the Serpasil period (3). The body weight increased in 15 of our patients from 1 to 19 pounds during the test period. In five it decreased from 1 to 12 pounds. There was no hypothermia. Laboratory examination of blood and urine (including C.B.C., N.P.N., Icterus Index, Thymol Turbidity Test, etc.) showed no pathological trend.

The best measure of the patients' progress proved to be the M.S.R.P.P. which was based on observations of a psychiatrist, a psychologist, and nursing personnel. The results reflect the patients' progress only in overt behavior. Qualitatively 18 of the 22 patients showed improvement; 9 of them showed marked improvement. Three patients showed no improvement, and one became worse. No correlation could be found between these results and diagnostic classifications, age, duration of illness, hospitalization, and the amount of drug given.

Five extremely disturbed patients could

TABLE 2

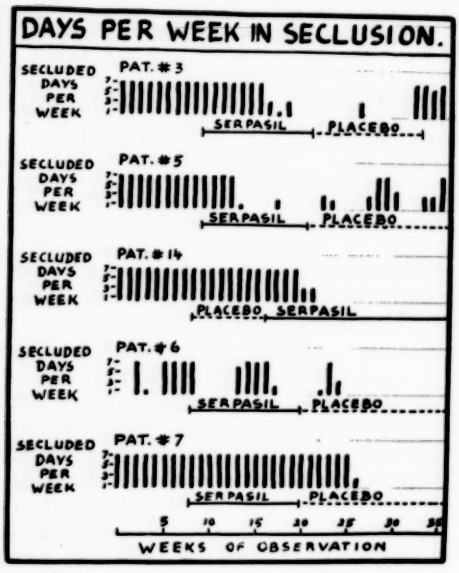


TABLE 3.—Levels of Significance Before and After Serpasil

| | Between Tests 1 and 2 | | Between Tests 2 and 3 | | Between Tests 1 and 3 | |
|---|---|---|---|---|---|---|
| | Right hand | Left hand | Right hand | Left hand | Right hand | Left hand |
| | % | % | % | % | % | % |
| Group 1 | | | | | | |
| Affect | 5* | | 5* | 5* | | 5* |
| Tone | | | 20† | | | |
| Anxiety | 5* | 5* | 5* | 5* | 10† | 10† |
| Group 2 | | | | | | |
| Aggression | | | | | 5* | 5* |

* Statistically significant.
† A trend.

leave their seclusion rooms (table 2). Patients nos. 3, 5 and 14 could be taken out of seclusion 4 to 7 weeks after the start of Serpasil medication. The record of patient no. 6, who was a constant "eloper", is not quite convincing as he was secluded only periodically. After the last week and a half in seclusion, five weeks after the end of Serpasil treatment, he could be kept on a general ward for 4 months. He is still out of seclusion but has been under Serpasil treatment again for the last seven weeks. The last patient on this table left the seclusion room 6 weeks after the end of Serpasil treatment. This delay may be the result of a lag in the action of the drug which was characteristic in some individuals under the dosage used in this experiment. In addition, this coprophagic, impulsively aggressive catatonic was feared by the nursing personnel to such an extent that for a period they were extremely reluctant to take him out of seclusion. This patient has maintained himself on the general ward for the last four months, the last two months with the help of renewed Serpasil medication.

Nine patients who were testable on the Wechsler-Bellevue Intelligence Scale, Form I, showed a gain of 8 to 25 points in the full scale I.Q. While these gains can be partially explained on the basis of practice effect, the authors felt they actually represented an increase in intellectual efficiency. Eight of 13 patients showed over-all improvement on the Rorschach and Figure Drawing Test.

Of the nine patients who were able to cooperate with the Mira Myokinetic Test, seven showed over-all improvement and two stayed the same. Thirteen were untestable. Table 3 reveals that in Group no. 1 anxiety was significantly lessened after administration of Serpasil. Quantitatively, psychomotor muscular tone improved in the placebo period following Serpasil. This improvement was not significant but nevertheless indicated a trend. Affect significantly improved after Serpasil. In Group no. 2 the only quantitative significant change was an over-all lessening of outward aggressive feelings and movements after Serpasil was administered. Qualitatively, the final results of the Mira are somewhat tentative and incomplete due to the difficulty in persuading the subjects to do the test all three times. Therefore, many of the t scores which would ordinarily be thought to be significant were invalidated due to the equal weighting of all scores, unscorable items and a constant change of the number of items completed. Of the 7 who improved on the Mira, the following features were noted: less anxiety, less aggression directed outwardly, improvement in muscular psychomotor tone, and better affectivity. There was more relaxation in muscular tone, less tendency to submit to gravity, yet less rigidity and tightness in musculature. The hand movements were not

TABLE 4.—Comparison of Morbidity Scores Obtained by Groups 1 and 2 on the M.S.R.P.P.

| Factors | 1st 6 wks. | | 2nd 6 wks. | | 12 wks. | | 1st 6 wks. | | 2nd 6 wks. | | 12 weeks | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 Pl | 2 Serp | 1 Pl | 2 Serp | 1 Pl | 2 Serp | 1 Pl | 2 Serp | 1 Pl | 2 Serp | 1 Pl | 2 Serp |
| Total morbidity | .80 | .40 | .02* | .30 | .01* | .20 | .60 | .10 | .80 | .05* | .50 | .02 |
| Retarded depression/manic excitement | .90 | .10 | .10 | .60 | .05 | .40 | .40 | .60 | .90 | .40 | .80 | .30 |
| Compliance/resistiveness | .90 | .60 | .05* | .40 | .10 | .40 | .40 | .02 | .50 | .60 | .10 | .80 |
| Paranoid projection | .80 | .40 | .10 | .05* | .10 | .40 | .70 | .80 | .70 | .40 | 1.0 | .80 |
| Activity level | .30 | .60 | .50 | .40 | .60 | .40 | .90 | .30 | .20 | .90 | .40 | .50 |
| Melancholy agitation | .70 | .20 | .05* | .20 | .05* | .05* | .30 | .60 | .10 | .05* | .40 | .30 |
| Perceptual distortion | .90 | .30 | .10 | .40 | .05* | .60 | .70 | .90 | .40 | .05* | .30 | .05* |
| Motor disturbances | .70 | .40 | .05* | .70 | .01* | .70 | .60 | .50 | .70 | .30 | .90 | .20 |
| Submissiveness/belligerence | .01* | .20 | .01* | 1.0 | .01* | .30 | .90 | .10 | 1.0 | .50 | .90 | .02* |
| Withdrawal | .30 | .80 | .60 | .30 | .80 | .90 | .90 | .70 | .90 | .50 | .90 | .30 |
| Self-depreciation/grandiose expansion | .30 | .80 | .05* | .80 | .70 | .30 | .60 | .30 | .60 | 1.0 | .80 | .20 |
| Conceptual disorganization | .60 | .30 | .02* | .60 | .01* | .60 | .40 | .20 | .40 | .50 | .40 | .10 |

* Statistically significant.

as expansive or grandiose, were more constricted in lateral and dorso-ventral movements and generally better controlled. Change took place especially in the right hand movements, which classically are supposed to represent conscious effort and control, while the left hand represents more unconscious feelings, thoughts, and attitudes. Often there were drastic changes in the direction of aggression, tone, anxiety and emotion.

## Discussion

On the whole, marked—sometimes dramatic—behavioral changes were observed in the severely disturbed patients. The most striking change was noted in the reduction of aggressiveness and combativeness as measured by the M.R.S.P.P., the Rorschach, Figure Drawing Test, Mira Myokinetic Test, and the records of hours in seclusion. There was a marked reduction in perceptual distortion as characterized by reduction in hallucinations, delusions, disorientation and obsessive hostile impulses. These changes are similar to those observed by Hollister *et al.* (5).

Basically, these changes were symptomatic in nature, and the structure of the illness remained unchanged. Psychological test data revealed little change in basic pathology but did indicate the reduction in anxiety and tension and increased control of hostile impulses. Our conclusions are essentially in agreement with Kirkpatrick and Sanders (6), who state that Serpasil "did not change mental processes but improved relevance and coherence." Although our experimental period was too brief to draw extensive conclusions as to the final effect of this mode of treatment, it is probable that the drug may be an effective adjunct to other therapies as it increases the accessibility of psychotic patients.

As previously noted, there is a lag between the administration of the drug and a noticeable psychological effect. The effect once obtained is sustained even after discontinuation of the drug. This sustained effect is variable; in some individuals it lasts but one week, while in others it extends over more than two months. It is our impression that the gradual increase in dosage over a considerable period of time is as effective as the rapid administration of high doses in chronically disturbed patients.

The gradual method of administration has other advantages as well. In our experimental group, a minimum of side reactions was observed. These patients did not complain of nasal congestion, gastrointestinal symptoms, nausea, vomiting or anorexia. Therefore, there was little difficulty in the administration of the drug, and the amount of nursing care necessary was drastically reduced.

Barsa and Kline (1) observed a period of "turbulence" in certain of their patients early in the administration of the drug. In a number of the patients in our experimental group similar reactions were observed. The period of excitement was temporary, and these patients eventually made marked improvement.

The results of the statistical treatment of the M.R.S.P.P. are shown in table 4. The differences of the means were calculated between rating scores obtained during various

periods of the experiment. The level of significance is given for the total morbidity and for 11 specific factors.

The differences of the mean between Groups 1 and 2 at the beginning of the experiment, though not shown on table 4, demonstrated that there was no significant difference (p equals .90) between the groups in regard to total morbidity or in regard to any of the 11 factors. In terms of the M.R.S.P.P., therefore, it can be assumed that the two groups are homogeneous. For the purposes of this scale p equals .05 was considered as the "cut off" point for significance.

There is a significant difference of the means obtained at the beginning of the Serpasil period and at the end of the Serpasil period on the total morbidity scale for both groups. The total morbidity scale represents a measure of the degree of deviant behavior in a given individual or group when compared with the typical psychotic population. The average total morbidity raw score of the entire experimental group was such (63.36) that the experimental group represents the upper two per cent of disturbed patients.

No significant difference in the degree of improvement obtained with Serpasil could be statistically demonstrated between Group 1 and Group 2, either at the mid-point of Serpasil or at the end of the Serpasil period. In other words, both groups improved approximately the same extent. While both groups showed parallel improvement during the Serpasil period in two factors (perceptual distortion and submissiveness versus belligerence), Group 1 showed improvement in other factors as well. The basis of this discrepancy could not be determined. There is a notable lag in the improvement after the administration of the drug. With the exception of the fact of submissiveness versus belligerence, no improvement was noted in either group until the second six weeks of the Serpasil period.

## Summary and Conclusions

1. Eighteen out of 22 severely disturbed chronic schizophrenics from the maximum security ward of a state hospital showed improvement under oral Serpasil treatment; half of them, marked improvement.

2. Clinical rating, psychometric, projective and expressive psychological tests basically agree on the effectiveness of the drug.

3. The authors feel that present psychological tests are not adequate for the quantitative evaluation of changes in severely psychotic patients.

4. Due to cautious increase of individual doses and adherence to oral medication, side reactions were minimal.

The authors acknowledge with thanks the invaluable aid of Sol Froshnider, Boris Gertz, Mitchell Karno, Arthur Lawson and Andrew Yang. They also wish to thank Drs. Lorr, Jenkins and Holsopple for permission to use their rating scale.

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# STUDIES ON MESCALINE

## VI. Therapeutic Aspects of the Mescaline-Chlorpromazine Combination[1]

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The use of mescaline as a therapeutic agent in psychiatry has been suggested by Stockings (16) and Guttmann (8). Hoch, Cattell, and Pennes (9) felt that many cases would have to be studied before any conclusions could be drawn. Cattell (1) has not found the drug to have any therapeutic value. Recently Hoch (10) stated that "the use of these two compounds (d-LSD$_{25}$ and mescaline) in therapy is still under investigation and its value for this purpose is not fully assessed." Sandison, Spencer, and Whitelaw (15) were favorably impressed with the therapeutic action of lysergic acid diethylamide.

Huxley's (11) statement, "But the man who comes back through the Door in the Wall will never be quite the same as the man who went out," suggests that mescaline produces some hitherto unknown insight. The same may be said of Marriott (12) who noted that "It's like seeing the door to life swing open." Auto-experiments with mescaline have shown that it is possible in a clear setting to recall and work through significant conflictual material.

Our initial results following treatment with mescaline and chlorpromazine have been reported briefly (2). This present study is an extension and elaboration of the initial note.

### Materials and Methods

Fifty-seven male and female patients, ranging in age from 16 to 60 years, were studied (table 1). The majority were schizophrenics (39 patients), and the others were distributed through eight diagnostic categories (table 2). They were divided into two groups, acute (40 patients) and chronic (17 patients), in accordance with the duration of illness and time interval between admission and treatment (tables 3–4). Fourteen (35%) of the 40 patients in the acute group and one (.06%) of the 17 in the chronic group were ill up to one year before admission. Eighteen (45%) acute patients and no chronic patients were treated within nine days of admission to the hospital (table 4). The earliest time of treatment after admission in the chronic group was two months and the latest 25 years, with the others spread in between this period. The acute patients were selected at random from the admission service, while the chronic group had been in residence at the hospital for many years.

On the morning of the test each patient received a light breakfast. A control electroencephalogram as well as subsequent recordings under mescaline was done in 15 patients. All patients cooperated for this study, and none refused the injections.

Mescaline sulfate (0.5 grams) was injected intravenously at the rate of 2 cc. per minute. Pulse, blood pressure, and pupillary diameters were recorded every 15 minutes wherever practicable. The patient was asked several standard questions as: "How do you feel?", "What are your thoughts?", and "What are you reminded of by this feeling or thought?" If any symptom was elicited, the patient was asked to associate his thoughts freely and recall any memories. The material offered was never interpreted. The patient was not asked any leading questions.

After one to one and one-half hours, the patient was given 50 mg. of chlorpromazine hydrochloride intramuscularly, and the interview continued for approximately one-half hour. At that time the procedure was terminated and the patient returned to the ward. He was interviewed in the afternoon and the next day. Psychotherapeutic sessions were held wherever possible once or twice a week.

All of the chronic patients received one treatment. Twenty-seven of the acute patients received one treatment and the others from two to 16 treatments (table 5).

[1] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

[2] Manhattan State Hospital, Ward's Island, New York 35, N. Y.

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TABLE 1.—AGE

| | Acute | Chronic |
|---|---|---|
| 11–19 | 5 | 0 |
| 20–29 | 12 | 2 |
| 30–39 | 15 | 4 |
| 40–49 | 6 | 8 |
| 50–59 | 1 | 3 |
| 60–69 | 1 | 0 |

TABLE 2.—CLINICAL DIAGNOSES

| | Acute | Chronic |
|---|---|---|
| Dementia praecox, paranoid | 6 | 9 |
| Dementia praecox, catatonic | 9 | 2 |
| Dementia praecox, mixed | 7 | 0 |
| Dementia praecox, hebephrenic | 1 | 3 |
| Dementia praecox, simple | 2 | 0 |
| Psychoneurosis | 7 | 0 |
| Involutional psychosis | 1 | 0 |
| Manic depressive, manic | 2 | 2 |
| Psychosis due to convulsive dis | 1 | 0 |
| Psychosis with psychopathic pers | 1 | 0 |
| Psychosis due to alcohol | 0 | 1 |
| Undiagnosed | 2 | 0 |
| Primary behavior disorder | 1 | 0 |

TABLE 3.—DURATION OF ILLNESS BEFORE ADMISSION

| Time | Acute | Chronic |
|---|---|---|
| To 1 yr | 14 | 1 |
| 1–3 yrs | 6 | 5 |
| 4–7 yrs | 6 | 1 |
| 8–11 yrs | 2 | 1 |
| 12–15 yrs | 3 | 3 |
| 16–19 yrs | 0 | 1 |
| 20–23 yrs | 0 | 2 |
| 24–27 yrs | 0 | 2 |
| 28–31 yrs | 0 | 1 |
| Unascer | 8 | 0 |
| Life | 1 | 0 |

TABLE 4.—TIME INTERVAL BETWEEN ADMISSION AND TREATMENT

| Days | Acute Patients | Chronic Patients |
|---|---|---|
| 1–5 | 10 | 0 |
| 6–9 | 8 | 0 |
| 10–14 | 7 | 0 |
| 15–20 | 5 | 0 |
| 21–24 | 5 | 0 |
| 25–29 | 1 | 0 |
| 30–50 | 3 | 0 |
| >51 | 1 | 17 |

TABLE 5.—TREATMENTS PER PATIENT—ACUTE

| Number of Treatments | Patients |
|---|---|
| 1 | 27 |
| 2 | 8 |
| 3 | 2 |
| 5 | 1 |
| 6 | 1 |
| 16 | 1 |

There were several control groups: *Acute patients:* Under identical conditions as the regular group, eight patients received mescaline followed by saline. *Chronic patients:* Seven patients received mescaline followed by saline. Nine patients received saline and chlorpromazine. Saline was substituted for mescaline and chlorpromazine in nine patients.

The protocols consisted of either verbatim notes taken at the session or transcriptions from a tape recorder. One of us was always present during the session with a nurse and occasionally one or two residents.

## RESULTS

The pulse rate accelerated under mescaline in 11 patients, slowed in six patients, and in no case was unchanged. The systolic blood pressure rose in seven patients, fell in three patients, and was unchanged in four. The diastolic blood pressure rose in seven patients, fell in four patients, and was relatively unchanged in three. These cardiovascular variations in the mescaline state were never severe although the diastolic blood pressure showed continued fluctuations. The change in blood pressure averaged plus or minus 20 mm. of mercury, and the pulse varied 10–30 beats. The pupillary diameter almost uniformly increased after the injection of mescaline with development of marked mydriasis. Exact pupillary measurements frequently could not be obtained since many patients were uncooperative. The cardiovascular and pupillary changes after chlorpromazine have already been reported elsewhere (3). Electroencephalographic changes during the mescaline-chlorpromazine state have been briefly noted (3) and already described in greater detail (13).

Fifteen (60%) of the successfully treated acute patients received the drug within nine days of admission while the others were treated between 10 and 50 days. Only three (20%) of

the unsuccessful acute patients were treated within these nine days.

*Acute patients:* At the onset of the mescaline-induced state the desire was expressed by almost all patients to "go to the bathroom", "to urinate", or "to move my bowels". After the injection of 1 cc. (0.025 grams) occasional patients would scream and shout, "I'm going crazy, I'm going crazy. This stuff makes me crazy." At the end of the injection, two patients made suicidal attempts. The general reactions to mescaline have been described before (4). Anxiety, tension, uneasiness and restlessness were the most frequent initial responses to the intravenous injection of mescaline and formed the background for the total response. The patients were frequently antagonistic, suspicious, hostile and occasionally aggressive. A little more than one-third showed inappropriate affect. Delusions and hallucinations were present in 17 and 22 patients, respectively. Fourteen patients became markedly lethargic during the procedure, while some were occasionally drowsy, and a few became sleepy. Panic, mutism, negativism, euphoria, silliness, nihilism, grandeur, unreality, depersonalization, fatigue, stereotypy, somnolence, irrelevant, incoherent and flighty speech were observed in some patients (chart 1).

While nausea was frequent and vomiting occasional, several patients retched and expectorated during the entire time under the influence of mescaline. Homosexual conflict or complete confusion of sexual identity was noted in the histories of these patients. A 21-year-old Puerto Rican male with a history of marked homosexual conflict became panic stricken as he looked at the syringe that was being used to inject the chlorpromazine at the end of the treatment. This patient had been nauseous, had retched, vomited and expectorated throughout the treatment.

The psychic response to mescaline tended to reflect the patient's general character structure. The passivity of several male and female patients was striking. They lie motionless on the bed during most of the procedure, were poorly productive or stereotyped in their responses, and showed no emotional reactions. This was particularly marked in two drug addicts, who experienced the mescaline state as similar to that induced by drugs. Two alcoholic patients compared it to "a hangover after a drunk". One said, "Coming off drunks; the nerves seem raw, jangly; you're filled with some such feeling. You throw up. You retch." On the other hand, mescaline released aggressive and hostile impulses that were directed outwardly either in a diffuse random fashion or towards one individual, usually the physician. He was then used as a symbol of feelings toward significant environmental figures. These potentially destructive impulses were accompanied by extraordinary discharges of feeling. Aggressivity and hostility most often seemed to be directed at a parent figure.

Sexual material was noted in 27 of 40 patients, either verbalized directly, given in an

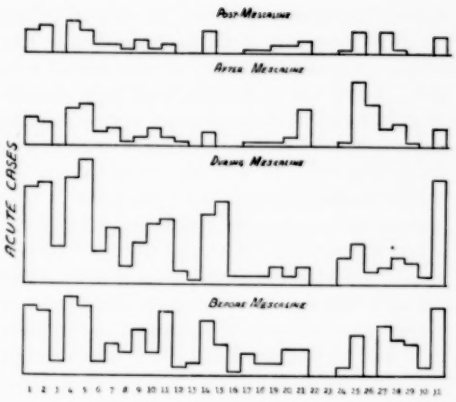


CHART I. (Data Available in 34 Patients.) Profile of symptoms shown by acute patients.

There is a sharp change in the profile between the pre- and post-mescaline periods.

*Key:*

1—Tension
2—Anxiety
3—Panic
4—Uneasiness
5—Restlessness

6—Mutism
7—Antagonism
8—Negativism
9—Suspicion
10—Hostility

11—Inappropriateness
12—Euphoria
13—Silliness
14—Delusions
15—Hallucinations

16—Nihilism
17—Grandeur
18—Unreality
19—Depersonalization
20—Bizarreness

21—Fatigue
22—Echolalia
23—Echopraxia
24—Stereotypy
25—Lethargy

26—Somnolence
27—Irrelevant
28—Incoherent
29—Flighty
30—Neologisms
31—Sexual Material

abstract symbolic manner, or demonstrated by movement and gesture of the body. The frequency and persistence of this sexual material during the treatment itself were impressive. It took the most unusual forms, such as pulling off the blood pressure cuff when it was being inflated ("It reminds me of masturbation; I masturbate with my right hand."). One patient said as the cuff was being inflated, "I heard a squeezing. It tensed me up." (What does this squeezing remind you of?) "The thought comes to me—breasts—tooth paste—a tube of tooth paste—squeezing my hand—probably masturbation." Leg and thigh movements were also noted ("When I have intercourse my feet move like this.") as well as generalized to and fro body movements and soft hand motions not unlike those of Hawaiian dancers. One patient, placed in an open restraint because of uncontrollable violence, bit and sucked furiously at the canvas about her neck. When asked what she was doing, she said, "It's the origin of the stock, you fool; it begins with a P." The number of patients displaying symptoms of tension, anxiety, panic, uneasiness or restlessness and the number of patients displaying sexual material were about the same (chart 1).

The emotional upheaval produced by mescaline can best be understood by the associations, "It was like an emotional brain wash", "a horror, a torture chamber", "an airplane ride", "a four engine transport on the flight line standing still with all four motors going", or a "planet whirling through space". It made many "think of things better left forgotten." Mescaline produced a flow of thought and feeling that for the most part could not be repressed. "One thought comes after the other so fast I can't get them out quick enough." Another said, "Before I finish one idea, another is already there. Crazy, isn't it?"

As the associations progressed, the subjective feeling of nausea or actual retching often followed the verbalization of conflictual material. A patient made mention of the Albany night boat. When asked to tell something about the Albany night boat ride she replied, "I feel nauseous."

Recall of childhood memories or return to an infantile body image was not evident. In the few cases where patients were asked a direct question to elicit this information, the reply was negative. The content of recalled events seemed to center more around adolescent and subsequent life situations.

Delusional material was noted in three patients after the treatment, and five the following day. Hallucinations disappeared in all patients following the treatment. Lethargy and somnolence were rather striking in the afternoon following the treatment, but this subsided within 24 hours.

The effects of the injection of chlorpromazine have already been reported elsewhere (3). Tension and anxiety began to subside within minutes following the injection. In most patients the whole mescaline-induced state disappeared in one hour. One patient required a second injection of 50 mg. of chlorpromazine to terminate the state. The intense push and flow of thought abated slowly, and many patients became lethargic, drowsy and sleepy. Some would ask to be left alone for awhile to sleep and to talk to the doctor afterwards. One said, "I'll tell you everything. Let's get off this plane. Get me out of here quickly. I'll talk to you quietly after I feel better and have a good night's sleep." Another said, "I feel very much alive now. I have an easier chance to breathe. So much easier, it feels good. It was worse than being seasick. You can always see the end of a voyage. I feel like I'd like to talk to you for hours now."

The clinical results following treatment are indicated in table 6. Eight of the 18 patients in a complete remission received follow-up psychotherapy. However, the clinical result was already apparent before this was begun. The results in patients of the acute group in complete remission were produced by a single treatment with mescaline-chlorpromazine in 13 patients, two treatments each in four patients, and 16 treatments in one patient (table 7). All abnormal thinking and feeling disappeared

TABLE 6.—Clinical Results

| | Acute | Chronic |
|---|---|---|
| Complete remission of symptoms | 18 | 0 |
| Improved | 1 | 3 |
| Partial improvement | 6 | 4 |
| Improvement with relapse | 4 | 0 |
| Unimproved | 11 | 10 |

TABLE 7.—ACUTE PATIENTS

| | Number of Treatments | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 16 |
| Complete remission | 13 | 4 | | | | | 1 |
| Improved | 1 | | | | | | |
| Partial improvement | 3 | 2 | | | 1 | | |
| Improved, then relapse | 1 | 2 | | | | 1 | |
| Unimproved | 9 | | 2 | | | | |

within one week of the treatment without recurrence during the hospital stay in 18 acute patients in complete remission. The improved and partially improved patients showed degrees of increase in feeling tone and decrease of abnormal ideation. Four patients in the acute group improved but relapsed within several days or weeks. One patient subsequently received insulin coma with poor results but then responded to chlorpromazine and left the hospital. One patient with a history of phobic behavior and "falling spells", an electroencephalogram consisting of high voltage slow waves and bursts, showed a complete remission of symptoms after the first treatment although the electroencephalogram was unchanged. He relapsed after 48 hours and then improved dramatically again after the second treatment; only to relapse again after 28 days. Further treatment was ineffective. The emotional component in two other patients was controlled with chlorpromazine, but the abnormal ideation persisted.

Positive or negative transference feelings towards members of the treatment group were expressed either openly or by symbolic gesture. The physician reminded one patient of her father, "He used to lock me in the room and I'd scream and bang on the door. I hate you like I hated him." The nurse was asked to leave the room by one patient because he could not talk about sex while she was there. Erotic feelings suggesting intimacy were displayed by many female patients. Some asked to "hold your hand" or "not to be left alone"; some were sullen, resentful, refused to answer and remained mute. The presence of several people in the room seemed to impede the flow of material and establishment of a therapeutic relationship. One of us in a personal mescaline experience wrote in the protocol, "I feel mentally undressed now and if anybody walks in I'll kick him out." The setting up of a tape recorder frequently led to an unproductive session. One patient said she felt like a "monkey in a zoo", and another wanted to know when we would be through "staring" at her.

It was not possible to predict the course of events after mescaline. There was no relationship between the general clinical state or diagnosis before mescaline and the subsequent results.

*Chronic patients:* The clinical display in these patients was essentially the same as in the acute group. Many of the symptoms, such as anxiety and tension, while present, showed none of the intensity of the acute group. There was no or little emotional discharge associated with the procedure. The emotional responses were vague and indefinite, rather a generalized feeling of discomfort than tied specifically to any particular thought. The chronic patients seemed to be detached from the entire procedure. The symptoms of anxiety, tension, panic, uneasiness and restlessness, as well as delusions and hallucinations, were present in more patients after the mescaline-chlorpromazine treatment than be-

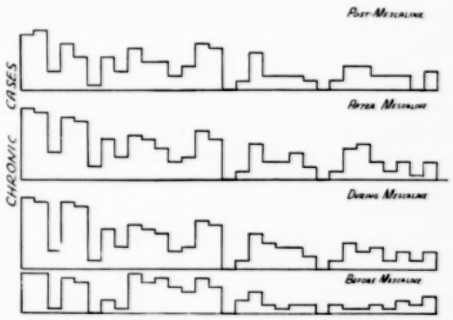


CHART 2. Profile of symptoms in chronic patients. The key to each bar is similar to chart 1. There is almost no change in the profile between the pre- and post-mescaline periods.

fore. Feelings of unreality and depersonalization increased after mescaline (chart 2).

The 25 control patients in the chronic group showed no clinical change whatsoever following the procedure. Five of the eight acute patients who received mescaline-saline showed various degrees of remission in their clinical state; three patients were unchanged.

## Discussion

Our frame of reference in this study has been that the clinical state induced by mescaline is neither an intoxication, a neurosis, nor a psychosis. It is a state of being in which the clinical spectrum ranges from sleep to murderous rage and from normality to thoroughly disorganized mental states. This wide sweep and lack of specificity in the mescaline-induced state do not really allow its designation by any single descriptive word (i.e., neurosis or psychosis). While the drug does in fact frequently produce a state indistinguishable from acute schizophrenia, it can also lead to states of tranquility. Previous authors have all very accurately described the clinical phenomena following mescaline but have failed to realize the wealth of hidden material to be uncovered by the free associations. The vivid color hallucinations can be viewed either as such, or in the following context as expressed by a female schizophrenic patient, "Red—it reminds me of my first menstrual period. I hated to be a girl. I wanted to be a boy." Cattell's inability to note any therapeutic effect after mescaline is partially due to the chronicity of his patients ("most of the patients had been treated with psychotherapy, many for years. . . ."), paralleling the poor results in our own chronic patients.

It is curious that under the effects of either mescaline or LSD, neurotic patients and normals recall early childhood memories. Yet, we were unable to elicit any similar recall in our own patients. This interesting problem is still under consideration.

It is a known fact that patients ill the shortest period of time and treated rapidly have the best prognosis. This is equally true in the present study.

Mescaline releases the repressing forces of the unconscious and permits a free flow of conflictual material hitherto kept out of awareness. The synthesis of feeling and thoughts results in resolution of conflict. ("I'll never love my father; at least, I won't hate him anymore.") The chlorpromazine permits the patient to see this new found material in a state of tranquility and in succeeding days to speak about his problems with calmness and ease. The exact role of chlorpromazine in this therapeutic technique is still open to question. The nature of its action at the cellular level is still unknown although it has been suggested that this substance as well as mescaline acts in the diencephalic area (5, 13, 14).

The increase of many symptoms in the chronic group following mescaline and in the post-mescaline period would support the concept that patients who are ill for long periods of time are poorly equipped to tolerate stress situations (i. e., mescaline).

The psychodynamic observations in the mescaline-induced state and their therapeutic applications will be considered elsewhere (6). The role of anxiety in the genesis of the mescaline-induced state and its relation to the therapeutic results are now under study (7).

At the present time, it is not possible to state if mescaline-chlorpromazine can alter the nuclear structure of the psychosis. The follow-up is still far too brief (11 months). At this writing (June, 1955) only one of the patients of the acute group discharged in a complete remission has been returned to the hospital. Two patients of the chronic group held their improvement, while the others relapsed.

The complete follow-up of patients in the acute group will be reported at a future date.

## Summary and Conclusions

1. The use of mescaline and chlorpromazine as a therapeutic technique has been described.

2. Eighteen of 40 acutely ill patients showed a complete remission of symptoms, and seven showed a partial improvement. Only seven of 17 chronically ill patients showed any improvement at all.

3. The therapeutic action was most marked in those patients who had been ill a short period of time before admission and were rapidly treated after admission.

4. Mescaline-chlorpromazine is most valuable as a therapeutic technique when used in a psychodynamic frame of reference.

The authors wish to thank Miss Selma Sterrn and Miss Dorothy Kauffman, R.N. (Manhattan State Hospital), Mrs. Yvonne Jensen and Mr. David Danielson (Central Islip State Hospital), for their cooperation throughout this study.

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# PRELIMINARY STUDIES OF THE METABOLISM OF LYSERGIC ACID DIETHYLAMIDE USING RADIOACTIVE CARBON-MARKED MOLECULES[1, 2, 3]

E. S. BOYD, E. ROTHLIN, J. F. BONNER, I. H. SLATER,[4] AND H. C. HODGE

Radioactive LSD-25 as prepared by Stoll, Rutschmann, and Hofmann (4) was used in these experiments. This compound contained radioactive carbon in the alpha position of each of the ethyl groups of the amide part of the molecule. The activity was such that 50 mg. of the crystalline material contained 270 microcuries. Since this is approximately 12,000 cpm./μg. and since the background of our counter is about 120 cpm., accurate counts could be obtained on samples as small as 0.01 μg. of LSD-25.

Rats were given 1 mg./kg. body weight of the labeled LSD-25 intraperitoneally and placed in a metabolism cage. The air entering the cage was dried and the carbon dioxide removed. The air leaving the cage was led through a series of carbon dioxide absorbers (potassium hydroxide solutions) arranged in such a way that the absorbers could be sampled at any desired time interval. Urine and feces were also collected. Rats were sacrificed at time intervals from 1½ to 12 hours after administration of the LSD-25, and the tissues were analyzed for radioactivity.

About 3½ per cent of the administered radioactivity was found in the expired air at the end of 12 hours (1). By this time the rate of expiration of labeled carbon had decreased to an insignificant value. The ratio of carbon 14 activity to milligrams of carbon dioxide (specific activity) in the various carbon dioxide traps indicated that all of the radioactivity exhaled was in the form of carbon dioxide. By the end of 12 hours about 3 per cent of the administered radioactive carbon had been excreted in the urine and only about 1 per cent in the feces. It should be noted that these figures and the following data on distribution in the tissues refer only to radioactive carbon and not to LSD-25. Other data, however, indicate that most of the radioactivity in all samples except expired air represents LSD-25 or metabolites not greatly altered chemically from the original molecule.

The distribution of radioactivity in most of the tissues of the rat in the period from 1½ hours to 12 hours after administration is fairly uniform; most of the tissues contain relatively similar, small concentrations of radioactivity. These concentrations seem to be interdependent and decrease slowly and proportionally over the 12-hour interval. Of the tissues analyzed, the liver and kidney tended to have higher concentrations and the brain and adipose tissue lower concentrations. The gut and its contents were the exception; together they contained 70 to 80 per cent of the dose at 3 and at 12 hours after administration.

These data give a clear picture of the over-all distribution. After intraperitoneal administration LSD-25 is picked up by the blood stream and is carried primarily to the liver where the LSD-25 and/or its metabolites are rapidly excreted into the bile. Only a fraction of the dose (probably 10 to 20 per cent) ever reached the systemic circulation in the rat. The LSD-25 and its metabolites which do reach the systemic circulation are fairly evenly distributed throughout the body. Some enterohepatic circulation of the LSD-25 and its metabolites between the liver and the gut would account for the fact that the level of radioactivity in the liver decreases only slowly from 1½ to 12 hours after administration.

A number of experiments was performed in which the bile ducts of female white rats were cannulated according to the method of Siperstein and Chaikoff (3). The rats were

[1] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

[2] From the Division of Pharmacology, School of Medicine and Dentistry, University of Rochester, Rochester, New York, and the Sandoz Company, Switzerland.

[3] This investigation was supported in part by a grant from the Geschickter Fund for Medical Research Inc.

[4] Present address: Eli Lilly and Company, Indianapolis, Indiana.

then given 1 mg./kg. body weight of the $C^{14}$-labeled LSD-25 intravenously, and the bile was collected for 3 hours. Two experiments in which the total radioactivity in the bile was determined showed an average of 64 per cent of the administered dose in the bile and 12 per cent in the contents of the gastrointestinal tract.

Several experiments were performed in which either the bile itself or an alkaline alcohol (2 per cent of 15 N ammonium hydroxide in absolute alcohol) extract of lyophylized bile was chromatographed on Whatman no. 1 paper in a n-butanol-acetic acid-water (6:1:5) system. The papers were then examined under ultraviolet light, and the fluorescent areas outlined, sprayed with Ehrlich's reagent (6), and counted in an apparatus similar to that described by Jones (2).

The chromatograms showed two distinct compounds with Rf values of 0.23 and 0.15 which were labeled M-1 and M-2 for reference purposes. There was also a spread of radioactivity in the region of Rf 0.6 to 0.9. The number of compounds represented in this spread is as yet uncertain, but it seems likely that at least one of them is unchanged LSD-25. The compounds M-1 and M-2 represent roughly 60 per cent of the total radioactivity in the bile. The infrared spectra of M-1 and M-2, as determined by the method of Toribara and DiStefano (5), are distinct from each other and from those of LSD-25, LAE (the monoethylamide), and lysergic acid. The compounds are compared in table 1 with LSD-25 on the bases of fluorescence, colors with Ehrlich's reagent, and Rf values.

The fluorescence of the metabolites and the colors with Ehrlich's reagent indicate that most of the ring structure of the parent compound is still intact. The radioactivity indicates that at least part of the diethyl side chain is still present. In addition, the decreased Rf values, in the system used, indicate an increased polarity in both of the compounds.

TABLE 1.—Comparison of LSD-25 with Two of its Metabolites

| Compound | Fluorescence | Color with Ehrlich's Reagent | Rf Value in Butanol-Acetic Acid-Water |
|---|---|---|---|
| LSD-25 | blue | violet | 0.83 |
| M-1 | blue | violet | 0.23 |
| M-2 | blue | blue | 0.15 |

A tentative identification of M-1 and M-2 in the urine of rats given 1 mg./kg. of LSD-25 intraperitoneally indicates that these metabolites may be distributed widely throughout the body.

The biosynthesis of radioactive ergot alkaloids was attempted. Rye plants were grown, and the flowers were inoculated with ergot spores. Thereafter the rye was placed in an atmosphere containing radioactive carbon dioxide while the ergot corms developed. The sclerotia exhibited a slight radioactivity, but the alkaloid content was extremely low. Grown in this way ergot alkaloids presumably would have random carbon 14 marking, both in the nucleus and in the side chain. Such molecules would provide the opportunity for an important comparison with the distribution of radioactivity following the administration of LSD with the radiocarbon in the side chain.

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# INVESTIGATION OF EFFECTS OF INTRAVENOUS RESERPINE IN DISTURBED PSYCHOTIC AND BRAIN-DAMAGED PATIENTS

## Electroencephalographic Correlation[1]

NANETTE DICE, M.D., B. K. BAGCHI, PH.D., AND RAYMOND W. WAGGONER, M.D.

The tranquilizing effect of reserpine was noted by Dr. Sibley Hoobler of the Cardiovascular Research Unit of the University Hospital and discussed with the members of the psychiatric staff. The "nothing bothers me" attitude which many of his anxious and tense patients developed suggested to him that the drug might be valuable in treating certain psychiatric patients. At the same time, reports were beginning to appear in the literature of the use of this drug elsewhere for this purpose. With the support of a commercial pharmaceutical company,[2] a research project was set up to study the effects of reserpine, both by oral and intravenous administration. We were interested in determining the effect of the drug as an emergency sedative and the possible benefit initiating treatment with the intravenous drug would have on a continued oral dose. We were also particularly interested in the effect the medication would have on brain-damaged children and on the acute organic brain syndrome of patients following electroshock therapy (EST).

The study was set up to utilize the intensive observation of a relatively small number of patients and was enlarged by including subjects from two neighboring institutions through the cooperation of the staff of these units.[3]

### SUBJECTS

Our subjects have been studied in 4 groups:

*Group I.* Acutely agitated adult patients: 9 subjects; age range 14–68; 6 men, 3 women.

*By diagnosis:*

| | |
|---|---|
| Schizophrenic reaction | 7 |
| Paranoid type | 4 |
| Acute | 2 |
| Catatonic | 1 |
| Manic-depressive reaction Hypomanic type | 1 |
| Senile psychotic reaction with cardiac decompensation | 1 |

*Group II.* Disturbed adult patients: 13 subjects; age range 18–71; 11 men, 2 women.

*By diagnosis:*

| | |
|---|---|
| Schizophrenic Reaction | 10 |
| Paranoid type | 6 |
| Schizo-affective | 2 |
| Acute | 1 |
| Undifferentiated with mental deficiency | 1 |
| Manic-depressive reaction Hypomanic type | 1 |
| Psychotic depressive reaction | 1 |
| Organic brain syndrome with depressive reaction and conversion features | 1 |

*Group III.* Brain-damaged children[4]: 20 subjects.

A. *Experimental group:* 10 subjects; white boys ranging in age from 8 years, 3 months to 15 years, 9 months.

Children's Service, Neuropsychiatric Institute... 2
Ypsilanti State Hospital.. 8

Subjects had been hospitalized from 9 months to 8 years and 8 months, with average hospital stay of 4 years.

B. *Control group:* 10 subjects; white boys ranging in age from 12 years, 5 months to 14 years.

All institutionalized at Wayne County Training School from 1 year to 5

[1] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

[2] Research carried out by courtesy and with financial support of the Upjohn Pharmaceutical Company.

[3] Ypsilanti State Hospital and Wayne County Training School.

[4] The diagnosis of brain damage was established by clinical history and the presence of such characteristic findings as hyperactivity, distractability, motor incoordination and psychological test findings.

years and 8 months, with average institutional stay of 4 years.

*Group IV.* Adult patients with acute organic brain syndrome, following a course of electroshock therapy: 13 subjects

A. *Experimental group:* 9 subjects; age range 20–55; 2 men, 7 women.
*By diagnosis:*
Psychotic depressive reaction..... 5
Schizophrenic reaction..... 4
No. EST: 8 to 15

B. *Control group:* 4 subjects; age range 20–33; 4 women
*By diagnosis:*
Schizophrenic reaction..... 4
No. EST: 11 to 14

## Procedure

### *Group I*

Observations were made by a special nurse and the psychiatric resident in charge of the patient.

1. Pre-injection pulse, blood pressure, respiration.
2. Injection of reserpine 2.5 mg. diluted to 5 cc. with 5 per cent glucose in water intravenously at the rate of 1 cc. per minute by the resident in charge of the patient.
3. Patient kept at bed rest whenever possible until blood pressure returned to pre-injection level, or until it stabilized.
4. Pulse, blood pressure, and respiration every 15 minutes for three hours or until the blood pressure returned to the pre-injection level; then every hour until stable; then every two hours until bedtime. Pulse, blood pressure and respiration with any unusual complaints and temperature with complaint of chill or fever.
5. Continuous behavioral record with time sequence.

### *Group II*

Observations were the same as in group I with the addition of:

1. A pre-injection electroencephalogram, one hour record, usually obtained the day of the first injection of reserpine intravenously.
2. Intravenous injection of reserpine usually given in electroencephalographic laboratory.
3. Continuous electroencephalographic record for 2 to 2½ hours immediately following the injection.
4. Daily intravenous administration of 2.5 mg. to 7.5 mg. reserpine for a total of 3 to 6 days.
5. Daily oral administration of reserpine 3.0 mg. starting the day following the intravenous injection and continuing for one month.
6. Electroencephalogram after one month oral reserpine.

### *Group III*

A. *Experimental group:* State Hospital patients were transferred to Children's Service, Neuropsychiatric Institute, for a five-day study which included:

1. Three days of observation during which psychiatric, physical, and neurological examinations were obtained as well as any further special examinations as indicated; daily basal pulse, blood pressure and respiration.
2. *Third day:* Pre-injection psychological study using Bender-Gestalt and three Wechsler subtests: Digit Span, Block Design and Picture Completion.
3. *Fourth day:* Pre-injection electroencephalogram; intravenous injection of reserpine 1.5 to 2.5 mg.; post-injection electroencephalogram; psychological retest, neurological reexamination. Observations of pulse, blood pressure, respiration and behavior were made as described for Group I.
4. *Fifth day:* Observation; beginning administration of reserpine 0.5 mg. two or three times a day orally; return to State Hospital.

Complete study included:

5. *One month:* Observation at State Hospital while continuing on oral reserpine.
6. Return for psychiatric reevaluation, psychological retest and electroencephalogram.

B. *Control group:*

The same psychological test battery was administered to selected children at Wayne County Training School.

2. Psychological retest in one month.

### *Group IV*

A. *Experimental group:*

1. Psychological test battery the afternoon of the last EST: Color Naming Test (10);

TABLE 1.—CLINICAL IMPRESSION

| Group | Improved | | | Unimproved | Worse | Total No. of Patients |
|---|---|---|---|---|---|---|
| | Markedly | Moderately | Slightly | | | |
| I | | 5 | | 3 | 1* | 9 |
| II | | 3 | 1 | 9† | | 13 |
| III | | | 5 | 4 | 1‡ | 10 |
| IV | | | | 9§ | | 9 |
| Total.. | Improved: 14 | | | Unimproved: 27 | | 41 |

* Felt subjective relief, but continued objectively disturbed, combative and delusional, with more active hallucinations; he fainted after getting up and walking post-injection.

† Five markedly agitated patients were not sufficiently controlled by the drug to complete the study. Three of these were started on EST before completion of the month trial on oral reserpine. All were transferred to State Hospitals. One severely depressed patient was started on EST after only 15 days of the oral drug.

‡ Patient with a diagnosis of narcolepsy.

§ No significant improvement in decreasing the acute organic brain syndrome was noted in patients given reserpine as compared to patients given no drug or a placebo.

Serial 7's (10); Hooper Visual Organization Test (5); Grassi Block Substitution Test (3); Wechsler Memory Scale (9).

2. Electroencephalogram the morning of the first post-EST day.

3. Injection of reserpine 2.5 mg. intravenously daily for three days.

4. Psychological retest the afternoon of the third post-EST day.

5. Electroencephalogram the morning of the fourth post-EST day.

B. *Control group:*

1. Electroencephalograms, psychological testing, observations as in the experimental group.

2. Injection of 5 cc. 5 per cent glucose in water instead of reserpine.

## RESULTS

*Side effects.* A. With the intravenous drug. In general, the response followed this pattern: facial flushing was noticed from 15 minutes to one hour post-injection; it became generalized and reached a maximum within the next hour. Nasal congestion occurred shortly after the onset of flushing. At the time of maximal flushing and nasal congestion, conjunctival injection appeared. Blood pressure fell from 15 to 25 mm. and pulse from 10 to 25 within 30 minutes to 2½ hours post-injection.

Additional side effects are listed in table 2.

*Side effects.* B. With the oral drug. Side effects were much less frequent than with the intravenous drug and included in order of frequency, nasal congestion, tiredness, fainting and increased bowel movements.

### *Electroencephalographic study*[5]

There were no significant changes in the immediate post-injection electroencephalograms in either Group II or III.

*Group II.* After one month, six of eight patients studied showed no electroencephalographic changes; two showed more bi-frontal, bi-premotor, and/or focal temporal slow waves than before.

*Group III.* Seven out of nine patients did not show any important electroencephalographic effect after a month. Significant bi-frontal and/or bi-premotor delta bursts were found in one patient, and more generalized theta slowing or accentuation of temporal theta focus with marked hyperventilation effect was found in another. Following withdrawal of the drug for one month in the first case strong bi-frontal delta bursts disappeared while other pre-reserpine electroencephalographic abnormalities did remain.

*Group IV.* Records were analyzed to determine whether the drug had any effect on electroencephalographic delta waves that always appear after EST. Four out of nine showed some decrease in the number of delta waves on the fourth day following EST, which could be expected even without the drug; two showed no change; one showed minimal increase and two showed moderate increase of deltas. The four post-EST control cases showed either no change or decrease of deltas.

### *Psychological testing*

*Group III. Analysis of Bender-Gestalt protocols:* Tests were administered by one examiner who gave them code names. A second examiner

[5] Of the adult pre-reserpine electroencephalograms, six were normal, six were borderline and seven were abnormal. Of the 10 children's pre-reserpine electroencephalograms, one was normal, three were borderline, and six were abnormal.

TABLE 2

| Code No. of Patient | Secondary BP Fall* | Dizziness | Anorexia or Nausea | Vomiting | Headache | Tremor | Chill | Fainting | Diarrhea |
|---|---|---|---|---|---|---|---|---|---|
| Group I | | | | | | | | | |
| 29 | | x | | | x | | | | |
| 30 | | | | | | | | | |
| 31 | | | | | | | | | |
| 32 | | | | | x | | | | |
| 33 | x | x | x | | x | | x | x | |
| 34 | | | | | x | | x | | |
| 35 | | | | | | | | | |
| 36 | | | x | | x | | | | |
| 37 | x | | | | | | | | |
| Group II | | | | | | | | | |
| 1 | | x | | | | x | | | |
| 2 | x | x | | | x | | | | |
| 3 | | | | | x | | | | |
| 4 | | x | x | | x | x | x | | |
| 5 | x | | | | x | | x | | |
| 6 | | | | | | | | | |
| 8 | x | x | | | | x | | | |
| 9 | x | | | | | | | | |
| 10 | | | | | | x | | | |
| 11 | x | x | | | | x | x | x† | |
| 12 | | x | x | | | | | | |
| 13 | | | x | | x | | x | | |
| 14 | x | | x | | | x | x | | x |
| Group III | | | | | | | | | |
| A | x | x | x | x | | | x | | |
| B | x | | x | | x | | | | |
| C | | x | x | x | x | | | | |
| D | x | | x | | | | | | |
| E | x | x | | | | | x | x | |
| F | | | x | x‡ | x | x | x | | |
| G | x | | x | x§ | x | x | | | |
| H | | | x | x | x | | | | |
| I | x | | x | | x | | | | |
| J | x | | x | x | x | | | x† | |
| Group IV | | | | | | | | | |
| Experimental | | | | | | | | | |
| 15 | x | | | | | x | | | |
| 16 | x | | | | | | | | |
| 17 | x | | x | | | | | | |
| 18 | x | x | x | x | x | | | | |
| 19 | x | x | x | x | x | | | | |
| 20 | x | x | x | | x | | | | |
| 21 | x | x | x | | x | | | | |
| 22 | x | x | x | | | | x | | |
| 23 | | x | x | | | | | | |
| Control | | | | | | | | | |
| 24 | | | | | | | | | |
| 25 | | | | | | | | | |
| 26 | | | | | | | | | |
| 27 | | | | | | | | | |

* Secondary blood pressure fall (several hours later) occurred in all groups; it appeared cyclic and usually accompanied by other symptoms as dizziness, faintness, headache, increased flushing, or nausea.

† Subjective faintness without loss of consciousness.

‡ Vomited three times, 1¾, 3 and 7 hours post-injection.

§ Vomited three times, 2¼, 3 and 7 hours post-injection.

rated the tests without knowing the time of administration or whether the individuals were in the experimental or control group.

In the brain-damaged children given intravenous reserpine, the psychological retest following the injection by 4 to 6 hours was given at a time when the children appeared sick. They were flushed, uncomfortable, some were nauseated and some were dizzy to the extent that the tests were administered to them in bed. At this time the Bender-Gestalt test showed constriction, better integration of the separate parts of the figure; slight improvement in consistency of drawing from left to right; but also some increased evidence of immaturity or regression in maturity level as judged by over-all comparison with Bender's chart (2).

By the end of the month on the oral drug, these children regained their previous maturity level and showed marked improvement in consistency of drawing from left to right, less integration of parts of figures, and a tendency toward expansion.

The control group showed relatively little change.

*Analysis of Wechsler subtest data:* Inspection of distributions reveals opposite tendencies in the two groups in Digit Span and Picture Completion tests. On the Digit Span test the experimental group scores tended to improve while the control group scores tended to become smaller. On the Picture Completion test the experimental group scores decreased while the control group scores tended to improve.

*Group IV.* In psychological testing there was no consistent change although when a decrease in intellectual deficiency occurred, it appeared to be greater in the experimental group than in the control group.

## Discussion

*Comparison of effect of intravenous reserpine in adults and children:* In general, there were more marked side effects in children than in adults. This was particularly true of nausea and vomiting. In Group II no vomiting occurred although four patients complained of anorexia, one felt hungry, and most had no difficulty following eating. Adults who were suffering from acute brain syndrome following EST had a higher incidence of nausea and vomiting. The high incidence of vomiting in brain-damaged children thus may be related to brain damage.

Seven out of 10 children showed an elevation of blood pressure occurring from 3¾ hours to 7½ hours after the injection of the drug. Three of the children were sleeping at the time of the elevated blood pressure reading. This rise in blood pressure was most dramatically shown by one 12-year-old boy who received 4.0 mg. reserpine instead of the usual 2.0 mg. Basal blood pressure and pulse were 118/72 and 80. Four hours and 20 minutes after the injection his blood pressure rose to a peak of 150/90; at this time he was flushed, perspiring and sleeping soundly. At seven hours, his blood pressure reached the lowest level of 110/60, and his pulse was 70; he was no longer sleepy and the flushing had faded. Adults have not shown a comparable elevation of blood pressure except one post-EST patient who complained of "light-headedness" at 9½ hours when her blood pressure was elevated to 138/74; pre-injection blood pressure had been 126/80.

*Postural hypotension:* Contrary to early reports that reserpine did not produce postural hypotension (8, 11, 12) we have found definite evidence that such a side effect occurs in many patients following intravenous administration of reserpine. This symptom was dramatically illustrated in a 15-year-old boy who was asked to sit up during the electroencephalographic recording two hours after the injection of 2.0 mg. reserpine intravenously. His blood pressure fell immediately from 115/60 to 84/55 but returned to 112/65 in the prone position. All post-EST patients given intravenous reserpine showed secondary blood pressure falls, usually after walking or sitting. One adult and one child fainted upon walking following the injection: the adult at 2¼ hours, the child at 5 hours post-injection.

*Series of daily intravenous injections:* When patients are given a series of daily intravenous injections of reserpine, their complaints and observable side effects tend to decrease progressively, while the sedative effect of the drug tends to increase progressively each day.

*Comparison of effects of intravenous reserpine and oral reserpine administered for one month:* Both side effects and sedative effect of reser-

pine are much more marked following an intravenous injection than during one month's oral administration of the drug. Only one patient has developed diarrhea following intravenous administration of the drug; this did not persist during subsequent injections or during the month on the oral drug. One boy developed increased frequency of bowel movements on the oral drug; he had not had diarrhea with the intravenous injection. Two adults were so distressed by side effects with the first intravenous reserpine injection that they refused further medication. No patient had enough discomfort on the oral drug that the drug had to be discontinued; the dose was reduced in one adult and two children.

*Electroencephalographic changes:* Our study indicates that reserpine does not produce any immediate electroencephalographic change in either adults or children even though there is marked autonomic effect in the form of flushing, nausea, etc. The latter manifestations are presumably central in origin. That the electroencephalogram is not changed by drugs that block sympathetic and parasympathetic ganglia is known. It was reported by one of us (1) that tetraethylammonium chloride (0.3 gm. intravenously) which produced in two or three minutes precipitous diastolic blood pressure drop in eight hypertensive cases of 26 per cent to 53 per cent did not cause any change in the electroencephalogram. It is also known that acute stress situations or situations when central autonomic centers are supposed to be activated usually produce apart from artifacts, non-specific fast activity rather than genuine slow activity in the electroencephalogram. However, seven of our subjects have shown increased slow activity.

*Psychological testing:* We are unable to determine on the basis of our data whether the improvement in integration and emotional control shown by our subjects on the Bender-Gestalt test is a function of the action of intravenous reserpine or whether it might occur under any situation of acute stress, particularly a situation involving similar physical discomfort.

The Wechsler subtests showed that the experimental group improved in auditory attention, while the control group improved in visual attention.

There was no correlation between decrement on psychological tests and increased abnormality of electroencephalograms. One patient who showed greater abnormality of electroencephalogram improved on psychological tests, while another patient with greater abnormality of electroencephalogram showed a decrement on psychological retests.

*Clinical results:* Our clinical results are not as optimistic as many previously reported by other investigators (4, 6, 7, 8). It appears that reserpine is not a panacea; it is of minimal value, if any, in brain-damaged individuals; its action varies greatly from patient to patient in disturbed psychotic individuals.

## Conclusions

1. As an emergency sedative drug, the effectiveness of intravenous reserpine varies greatly from patient to patient.

2. In a one-month study of ten brain-damaged children, five were slightly improved, five were unimproved.

3. Intravenous reserpine produced no significant effect upon the post-EST acute organic brain syndrome in nine patients.

4. Children and adults with organic brain syndrome showed greater side effects from intravenous reserpine; this was particularly true of nausea and vomiting.

5. Most brain-damaged children showed an unexplained rise in blood pressure occurring from 3¾ to 7½ hours after intravenous injection of reserpine.

6. Postural hypotension occurred in both adults and children up to 16 hours post-injection.

7. With a series of daily intravenous injections of reserpine, side effects decreased progressively while sedative effects increased progressively.

8. Continuous electroencephalograms for 2 to 2½ hours following intravenous reserpine showed no significant change from the pre-reserpine records but after one month on oral reserpine showed increased slow activity in four out of 17 patients. Electroencephalograms in post-EST patients after three daily injections of intravenous reserpine showed increased slow activity in three out of nine patients.

9. Psychological findings were inconclusive.

Trends were observed in children toward improved integration and emotional control, but also toward regression with the intravenous drug with some suggestion of improvement in auditory attention and restoration of maturity level, but loss of integration and emotional control with the oral drug.

10. Further study of the types of patients, methods of administration, and dosage in the use of this drug is necessary.

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# PHARMACOTHERAPY IN CHILDREN WITH PSYCHIATRIC ILLNESS[1]

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In the last half century and particularly in the last two decades advances in pharmacological therapy in medicine have been noteworthy and, in certain instances, spectacular. Antibiotics, sulfonamides, liver extract, hydantoin compounds, to mention only a few, have wrought impressive changes in clinical practice. Knowledge in basic chemistry and pharmacology has also increased markedly. Yet, the application of this new information has had, until very recently, very little utilization in the field of psychiatry. During the past year, with the introduction of chlorpromazine and reserpine, there has been a renaissance in drug therapy for the mental disorders.

During the past three years an exploratory study of pharmacotherapy has been conducted on the Children's Service of the Psychiatric Division of Bellevue Hospital and the Department of Psychiatry, N. Y. U. Bellevue Medical Center. The primary purpose of this study was to screen and evaluate drugs that might be helpful in the treatment of psychiatrically disturbed children. Secondly, a methodology was to be developed to investigate effectively the value of promising drugs. Thirdly, it was hoped that by the use of drugs of known action some knowledge could be obtained of the physiological abnormalities that accompany or cause mental disorders in children.

Prior to 1952, studies of drug therapy in psychiatric disorders of children had been principally confined to compounds of the hydantoin and amphetamine groups. In 1941 Bradley and Bowen (4) treated 100 children with benzedrine sulphate. Fifty-four per cent became "physically and emotionally, but not intellectually", subdued. Nineteen per cent were stimulated to better integrated and useful behavior. Twenty-one per cent were unaffected and 7% retrogressed. The only group that showed no improvement was that of structural defects of the brain. Subsequently, similar results were reported by Bradley (5) with dexedrine sulphate. This study was confirmed shortly thereafter by Bender and Cottingham (1) who reported an over-all improvement in 58% of cases treated with benzedrine. The improvement was marked in those cases diagnosed as psychoneurotic and neurotic behavior disorders and in the area of behavior and relationships. These authors did not perceive any improvement in those cases diagnosed as psychopathic personality, schizophrenic or organic.

There has been particular interest in drug therapy of children with behavior disorders who are known to have abnormal electroencephalographs. There have been a number of studies of the effectiveness of the hydantoin compounds in this group of children. Brown and Solomon (6), who used dilantin sodium, reported improvement in three of seven delinquent children with serious behavior problems and abnormal electroencephalographs characteristic of psychomotor epilepsy.

In a similar study by Walker and Kirkpatrick (13), all of 10 children with behavior problems and abnormal electroencephalographs showed improvement with dilantin sodium. Pasamanick (11), with the aid of several independent observers, carefully studied 21 children with psychiatric disorders. Fourteen of the children were diagnosed as primary behavior disorders, and the remaining seven had other psychiatric diagnoses other than schizophrenia. All of the 21 children were found to have abnormal electroencephalographs. Several drugs were administered to this study group. The effectiveness of anticonvulsant medication, such as dilantin sodium, Mesantoin and Tridion, was uniformly disappointing. Little benefit was observed with

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the use of phenobarbital. However, four out of 10 children had marked or unequivocally beneficial results with Amphetamine. Pasamanick concluded that Amephetamine was the only one of the drugs he evaluated which could be considered of therapeutic value in the treatment of child behavior disorders.

Since the beginning of drug studies on the Children's Psychiatric Ward of Bellevue Hospital, progress reports on the use of Elixir Benadryl (7) and Elixir Tolserol (8) have been written. The results with thse two drugs will be incorporated in the total report below.

Several papers have appeared concerning the use of Thorazine and Serpasil in children. There have been several reports of the use of chlorpromazine in connection with other drugs in hibernation techniques in young infants in acute severe physical illness or acute encephalitis. Heuyer *et al.* (10) have reported the use of chlorpromazine in seven children with psychomotor excitation. He reported a calming effect which lasted as long as the drug was administered. In only one case did the effect persist after the withdrawal of the drug. The maximum dosage used was 2 mg. per kg., but it was felt that higher doses might have been tolerated. The authors felt that in cases of chronic excitation this drug is of value in causing temporary sedation that might be prolonged at will in order to carry out psychotherapy or to bring about a lull while the child is in a family environment or with groups of children.

Gatski (9) has treated nine severely disturbed and chronically acting-out, emotionally maladjusted children with chlorpromazine, 40 to 80 mg. orally per day, for periods of three to four weeks. Within a week, the children showed improvement in social behavior and became more amenable to supervision and psychotherapy. The improvement disappeared when placebos were substituted.

Talbot (12) has reported the use of reserpine in irritable and hypertonic infants.

## Procedure

This entire study was performed on children who were admitted to the Children's Ward in Bellevue. Thus, this is exclusively a study of in-patient children. A general description of the patient load and conduct of this service has already been given (2, 3).

Patients for the study were selected at random from the children between the ages of seven and twelve who were admitted to the Ward. Although at first a few female children were included in the study, because of the preponderance of boys on the Ward, it was subsequently limited to boys. A total of 195 children has been studied in this program. The sample used is indicated in table 1.

Children were observed on the Ward from 10 to 15 days until they were thought to have arrived at a relatively steady state of behavior. During this period they were observed closely by all members of the staff, including senior psychiatrists and house staff psychiatrists, nursing staff, school teachers, recreational instructors and psychologists. Both during this preliminary period and during the period when the children were on drugs, they were evaluated by all of the members of the staff who had contact with them on special forms by a scaling system. Each child was evaluated in eight categories by each observer:

1. Motor activity.
2. Manifest anxiety.
3. Relationship problems with other children.
4. Relationship problems with adults.
5. Affect.
6. Motility.
7. Phantasy life.
8. Pathognomonic symptomatology, i.e., introjected bodies and hallucinations.

Each of the first five categories is scored according to a five-point scale, as follows:

— — representing marked hypoactivity, marked anxiety, severe relationship problems

TABLE 1.—Samples Used in Analysis of Drug Therapy

| Drug Administered | Diagnosis | | | |
|---|---|---|---|---|
| | Schizophrenic | Organic | Behavior disorder | Total |
| Benadryl | 21 | 13 | 8 | 42 |
| Ambodryl | 8 | 5 | 5 | 18 |
| Thorazine | 14 | 8 | 10 | 32 |
| Tolserol | 8 | 5 | 9 | 22 |
| Artane | 14 | 6 | 5 | 25 |
| Serpasil | 10 | 8 | 8 | 26 |
| Placebo | 13 | 7 | 10 | 30 |
| Total | 88 | 52 | 55 | 195 |

with other children, severe relationship problems with adults, marked depression;

− representing a moderate degree of hypoactivity, anxiety, relationship problems with other children, relationship problems with adults, and moderate depression;

0 representing the usual amounts of psychomotor activity, anxiety, relationship problems with children and adults anticipated on the service, normal affect;

+ representing moderate hyperactivity, somewhat less than the usual amount of manifest anxiety observed, moderately better relationship with other children and adults, and a moderate degree of elation;

++ representing excessive hyperactivity, marked freedom from anxiety in all situations, remarkable freedom from problems with other children and adults, and euphoria.

The other three categories are described as observed.

Having been observed on the Ward, each child was placed on one of the test drugs or one of the placebos. Drugs were labelled only by letter, and none of the observers was aware of whether drug or placebo or which drug had been prescribed. The child was kept on the drug or placebo for a period of four weeks with increasing doses of the drugs.

The drugs used were Elixir Benadryl, Elixir Tolserol, Elixir Artane, Elixir Ambodryl, Thorazine Hydrochloride tablets and syrup, and Serpasil tablets.[4] In table 2 the drugs are listed, and the initial and maximum dose for each is given. Observations were continued throughout the test period, and then the child was taken off the drug. By far and large, children were discharged or transferred at this point. However, when the child remained at the hospital after the four-week period, he was observed further. Where possible, electroencephalographs and a battery of psychological tests, including Wechsler-Bellevue, Bender-Gestalt, Goodenough drawings, the Mira test, and tests of manual coordination, were administered before and during the drug period. These tests were administered to all the children except those receiving Serpasil,

[4] Drugs were kindly supplied by the following companies: Elixir Benadryl and Ambodryl, Parke-Davis & Co., Detroit, Michigan; Thorazine, Smith, Kline & French, Philadelphia, Pa.; Elixir Tolserol, E. R. Squibb & Sons, New York, N. Y.; Elixir Artane, Lederle Laboratories, Peart River, N. Y.

TABLE 2.—Minimum and Maximum Daily Dosage Used in Drug Therapy

| Drug | Daily Dose, First Week | Daily Dose, Fourth Week |
|---|---|---|
| | *mg.* | *mg.* |
| Benadryl | 30 | 160 |
| Ambodryl | 30 | 160 |
| Thorazine | 30 | 100 |
| Tolserol | 1,000 | 4,500 |
| Artane | 2 | 12 |
| Serpasil | .3 | 3.0 |

Thorazine and one-third of those receiving placebos. When all the observations were completed, the composite observations of change in each category were evaluated on a five-point scale:

++ marked improvement;
+ moderate improvement;
0 none or slight change;
− moderate aggravations;
−− marked aggravations.

Children on the drug program were not treated differently from other children on the Ward; they participated in all the programs, recreation, school, etc. Since many of the children on the Ward received medication anyway, this test group was not particularly differentiated in this respect. For example, since many of the children are malnourished, multivitamin capsules are distributed quite widely.

## Results

In table 3 there is indicated the percentage of cases in each diagnostic group showing changes in behavior from drug treatment and also a summation in which the groups are combined. It is recognized that in certain of the groups, due to the smallness of the series, percentages are not valid, but this presentation makes for easier comparison.

It can be readily seen that the outstanding results are obtained with Benadryl in those cases diagnosed as primary behavior disorder, and with Tolserol in those cases diagnosed as organic brain disease. In both of these instances all of the concerned cases showed improvement. The administration of Thorazine helped half of the children with primary behavior disorders, but this is not noteworthy when compared to the 40% who showed improvement with placebo. In the organic cases, 50% of the patients receiving Thorazine, 46%

TABLE 3.—Per Cent of Cases in Each Diagnostic Group Showing Changes in Behavior from Drug Treatment

| Drug | Improved | Unchanged | Adversely Affected | Number of Cases |
|---|---|---|---|---|
| *Schizophrenic Cases* | | | | |
| Benadryl | 52 | 38 | 10 | 21 |
| Ambodryl | 38 | 38 | 25 | 8 |
| Thorazine | 57 | 29 | 14 | 14 |
| Tolserol | 38 | 50 | 12 | 8 |
| Artane | 43 | 21 | 36 | 14 |
| Serpasil | 40 | 60 | 0 | 10 |
| Placebo | 38 | 38 | 23 | 13 |
| *Organic Cases* | | | | |
| Benadryl | 46 | 54 | 0 | 13 |
| Ambodryl | 0 | 60 | 40 | 5 |
| Thorazine | 50 | 25 | 25 | 8 |
| Tolserol | 100 | 0 | 0 | 5 |
| Artane | 33 | 33 | 33 | 6 |
| Serpasil | 38 | 50 | 12 | 8 |
| Placebo | 14 | 71 | 14 | 7 |
| *Primary Behavior Disorder Cases* | | | | |
| Benadryl | 100 | 0 | 0 | 8 |
| Ambodryl | 40 | 40 | 20 | 5 |
| Thorazine | 50 | 40 | 10 | 10 |
| Tolserol | 33 | 67 | 0 | 9 |
| Artane | 20 | 60 | 20 | 5 |
| Serpasil | 38 | 50 | 12 | 8 |
| Placebo | 40 | 50 | 10 | 10 |
| *Groups Combined* | | | | |
| Benadryl | 58 | 36 | 6 | 42 |
| Ambodryl | 28 | 44 | 28 | 18 |
| Thorazine | 53 | 31 | 16 | 32 |
| Tolserol | 50 | 45 | 5 | 22 |
| Artane | 36 | 32 | 32 | 25 |
| Serpasil | 40 | 54 | 6 | 26 |
| Placebo | 33 | 50 | 17 | 30 |

receiving Benadryl, 38% receiving Serpasil, and 33% receiving Artane showed improvement, as compared with 14% improving with placebo.

It should be noted that one-third of the cases receiving Artane and one-fourth receiving Thorazine were adversely affected by these drugs.

In the schizophrenic group, no drug could be said to be outstanding in its over-all effect. Thorazine was best, improving 57% of the cases, and Benadryl was close behind, helping 52% of the children. The others show results scarcely different from the 38% who improved while receiving placebo.

When all the groups are combined, the Benadryl and Thorazine showed the best

TABLE 4.—Changes in Five Behavior Categories Accompanying Treatment with Different Drugs

(Per cent of Cases Changed)

| Drug | Improved | Normality Maintained | Unimproved | Aggravated |
|---|---|---|---|---|
| *1. Hyperactivity* | | | | |
| Benadryl | 29 | 20 | 49 | 2 |
| Ambodryl | 22 | 0 | 64 | 14 |
| Thorazine | 41 | 41 | 12 | 6 |
| Tolserol | 27 | 5 | 64 | 5 |
| Artane | 24 | 0 | 56 | 20 |
| Serpasil | 19 | 50 | 31 | 0 |
| Placebo | 13 | 33 | 47 | 7 |
| *2. Manifest Anxiety* | | | | |
| Benadryl | 54 | 2 | 42 | 2 |
| Ambodryl | 22 | 0 | 69 | 9 |
| Thorazine | 38 | 0 | 56 | 6 |
| Tolserol | 41 | 0 | 55 | 5 |
| Artane | 20 | 0 | 60 | 20 |
| Serpasil | 31 | 0 | 61 | 8 |
| Placebo | 27 | 0 | 66 | 7 |
| *3. Relationship Problems with Peers* | | | | |
| Benadryl | 44 | 0 | 55 | 5 |
| Ambodryl | 11 | 0 | 75 | 14 |
| Thorazine | 41 | 0 | 53 | 6 |
| Tolserol | 50 | 0 | 41 | 9 |
| Artane | 40 | 0 | 20 | 40 |
| Serpasil | 27 | 0 | 69 | 4 |
| Placebo | 27 | 0 | 60 | 13 |
| *4. Relationship Problems with Adults* | | | | |
| Benadryl | 56 | 0 | 39 | 5 |
| Ambodryl | 22 | 0 | 69 | 9 |
| Thorazine | 38 | 0 | 53 | 9 |
| Tolserol | 45 | 0 | 50 | 5 |
| Artane | 20 | 0 | 52 | 28 |
| Serpasil | 19 | 0 | 81 | 0 |
| Placebo | 27 | 0 | 73 | 0 |
| *5. Depressed Affect* | | | | |
| Benadryl | 37 | 0 | 63 | 0 |
| Ambodryl | 0 | 0 | 95 | 5 |
| Thorazine | 9 | 0 | 75 | 16 |
| Tolserol | 32 | 0 | 64 | 5 |
| Artane | 16 | 0 | 64 | 20 |
| Serpasil | 8 | 0 | 92 | 0 |
| Placebo | 10 | 0 | 87 | 3 |

results, the Benadryl indicating improvement in 58% of the cases, while the Thorazine in 53%. The Tolserol helped half of the children studied. The Ambodryl, Artane and Serpasil yielded results close to the 33% of children who showed improvement while receiving placebo. It is noteworthy that 32% of the cases receiving Artane and 28% of those receiving Ambodryl were adversely affected by these drugs.

In table 4 the data are broken down into five behavior categories. No noteworthy changes were observed in the areas of motility, phantasy life and pathognomonic symptomatology. Consequently, the results in these three areas are not tabulated. In the area of hyperactivity, the best results were obtained with Thorazine. Forty-one per cent of the total Thorazine group showed improvement with this drug. It should be noted that only 59% of the Thorazine group displayed hyperactivity as a significant pre-drug symptom; that is to say, 69% of the children in whom hyperactivity was a problem improved in this area with Thorazine. None of the other drugs was helpful in the reduction of hyperactivity. Also, none of the drugs was helpful in the stimulation of hypoactive, retarded children.

In the area of manifest anxiety, the best results were obtained with Benadryl, which helped 54% of the children to whom it was administered. As with anxiety, Benadryl was the outstanding drug in the area of relationship problems with adults and in alleviating depressed affect. Tolserol was best in helping relationship problems with peers although it was closely followed by Benadryl, Thorazine and Artane.

In order to establish the significance of these results, the drug data were compared with placebo treatments by means of the chi-square test. The results are indicated in table 5.

In the area of hyperactivity, the improvement noted with Thorazine is significantly different from placebo, to the level of .01. In the area of manifest anxiety, Benadryl is significantly differentiated, to the level of .01 also. Similar results with Benadryl are found in the area of relationship problems with adults and alleviating depressed affect. No drug was found to be significantly different from placebo in improving relationship problems with peers.

When all categories are combined, the only drug that yields results significantly different

TABLE 5.—Comparison of Results of Drug with Placebo Treatments

| Treatment | Improved | Number of Cases | | Different from Placebo | |
|---|---|---|---|---|---|
| | | Unchanged | Adversely Affected | Chi-Square* | Level of significance† |
| *Hyperactivity* | | | | | |
| Benadryl | 13 | 21 | 1 | — | — |
| Ambodryl | 4 | 11 | 3 | — | — |
| Thorazine | 13 | 4 | 2 | 7.36 | .01 |
| Tolserol | 5 | 15 | 1 | — | — |
| Artane | 6 | 14 | 5 | — | — |
| Serpasil | 5 | 8 | 0 | — | — |
| Placebo | 4 | 14 | 2 | | |
| *Manifest Anxiety* | | | | | |
| Benadryl | 23 | 17 | 1 | 7.34 | .01 |
| Ambodryl | 4 | 12 | 2 | — | — |
| Thorazine | 12 | 18 | 2 | — | — |
| Tolserol | 9 | 12 | 1 | — | — |
| Artane | 5 | 15 | 5 | — | — |
| Serpasil | 8 | 16 | 2 | — | — |
| Placebo | 8 | 20 | 2 | | |
| *Relationship Problems with Peers* | | | | | |
| Benadryl | 19 | 21 | 2 | — | — |
| Ambodryl | 2 | 13 | 3 | — | — |
| Thorazine | 13 | 17 | 2 | — | — |
| Tolserol | 11 | 9 | 2 | — | — |
| Artane | 8 | 9 | 8 | — | — |
| Serpasil | 7 | 18 | 1 | — | — |
| Placebo | 8 | 18 | 4 | | |
| *Relationship Problems with Adults* | | | | | |
| Benadryl | 25 | 15 | 2 | 6.22 | .01 |
| Ambodryl | 4 | 12 | 2 | — | — |
| Thorazine | 12 | 17 | 3 | — | — |
| Tolserol | 10 | 11 | 1 | — | — |
| Artane | 5 | 13 | 7 | — | — |
| Serpasil | 5 | 21 | 0 | — | — |
| Placebo | 8 | 22 | 0 | | |
| *Depressed Affect* | | | | | |
| Benadryl | 16 | 26 | 0 | 5.70 | .01 |
| Ambodryl | 0 | 17 | 1 | — | — |
| Thorazine | 3 | 24 | 5 | — | — |
| Tolserol | 7 | 14 | 1 | — | — |
| Artane | 4 | 16 | 5 | — | — |
| Serpasil | 2 | 24 | 0 | — | — |
| Placebo | 3 | 26 | 1 | | |

TABLE 5.—(CONTINUED)

| Treatment | Improved | Number of Cases | | Different from Placebo | |
|---|---|---|---|---|---|
| | | Unchanged | Adversely Affected | Chi-Square* | Level of significance† |
| *General Behavior (All Categories)* | | | | | |
| Benadryl | 25 | 15 | 2 | 4.03 | .05 |
| Ambodryl | 5 | 8 | 5 | — | — |
| Thorazine | 17 | 10 | 5 | — | — |
| Tolserol | 11 | 10 | 1 | — | — |
| Artane | 9 | 8 | 8 | — | — |
| Serpasil | 10 | 14 | 2 | — | — |
| Placebo | 10 | 15 | 5 | | |

* Unchanged and Adversely affected are combined. One degree of freedom throughout. No entries made for chi-square with probability value greater than .05.

† One-tailed test of significance since drug is hypothesized as better.

from the placebo is Benadryl and this only at the .05 level. While it is not indicated in the chart, when improvement with individual diagnostic categories is compared with placebo, only the children diagnosed as cases of primary behavior disorders and treated with Benadryl display statistically significant improvement when compared to the placebo group to the level of .01 by the chi-square test.

No significant change was noted in the battery of psychological tests before and during drug therapy that could be ascribed to the drug.

## DISCUSSION

It is quite evident that, with proper choice, pharmacological therapy can be of great help in the management of emotionally disturbed children in an in-patient setting. This is particularly evident with the results obtained with Benadryl, Thorazine and Tolserol.

The Benadryl appears to be most satisfactory in the therapy of primary behavior disorders, especially in those patients who show considerable manifest anxiety. In addition, Benadryl is of significant value in the over-all therapy of disturbed children, regardless of diagnosis. The major therapeutic effect of Benadryl appears to be its effect in reducing anxiety and subsequently improving relationship problems to adults and alleviating depressed affect where it exists. Elixir Benadryl has been widely used on the Bellevue Children's Service since the original research three years ago. Evidence that cannot be statistically validated confirms the impression of its value. It has been the feeling of the staff that ward management has been easier although the nursing and attending staff has been sharply decreased. The number of children necessitating transfer to the adult ward, housing very disturbed patients, has also decreased.

It should be noted that very few of the children on the ward at one time are on the research drug program. However, many of the other children, particularly girls or children below the age of seven, would be treated with Benadryl. In the research series, only one child displayed some somnolence with the Benadryl. This was a boy who was diagnosed as having an organic brain syndrome.

The Thorazine seemed to be useful in hyperkinetic children. It was our impression that it was particularly useful in hyperactive schizophrenic children. Of six schizophrenic children in whom hyperactivity was noteworthy, at the time of drug administration five showed improvement. The group is too small for statistical validation. However, if this trend should continue in a larger series, it would be significant. Hyperkinetic children in other diagnostic categories did not improve as impressively as the schizophrenic.

The impression of the value of Thorazine in the hyperkinetic, agitated schizophrenic was confirmed in a group of five patients thus diagnosed. These were cases that were so agitated at the time of their admission that therapy could not be delayed and an observation period was impossible. Two of these children were injuring themselves. The procedure followed in these cases was to administer an intramuscular injection of 25–50 mg. of Thorazine promptly and follow with oral dosages up to 150 mg. per day. In two of the cases, the injection of the Thorazine produced sleep for several hours. In all cases there was a reduction in agitation and a reduction in the distress caused by stimuli that otherwise would be perturbing. However, in this group of five children and in the larger series, there seemed to be a narrow margin between therapeutic usefulness and hypnosis. It was difficult

to achieve a point at which there was marked diminution of distressing symptoms and yet leave the child fully aware and alert throughout the day. At a dosage of 100 mg. Thorazine in the reported series and at 150 mg. in the group of five particularly agitated children outside the series, the patients tended to be somnolent part of the time.

The effect of the Thorazine appears to diminish with time, not only in the reported series but in other children who were carried for considerable periods of time in which dosages were steadily increased. After a period of six to eight weeks, improvement no longer was obtained. The Thorazine appeared to be particularly helpful in tiding children over a very difficult, acute situation upon admission until the diagnosis could be made or other therapy, such as electroshock therapy, could be administered. Benadryl has been used similarly, but it did not appear to be as effective in the very agitated hyperkinetic child as the Thorazine within the dosage limits that were used.

Three children of the 30 who received Thorazine developed skin rashes. In two cases the rash was ascribed to the Thorazine. The other one was questionable since it occurred at a time when there was an epidemic of German Measles on the ward and this might have been a transitory case.

Elixir Tolserol appeared to be useful in the therapy of children with behavior disorders resulting from organic brain disease. Due to the smallness of this series, five, this cannot be statistically validated. However, if this trend should continue in a larger series, it would become statistically valid. It was the impression that the children appeared to gain control over their impulses and to be better integrated through this drug. Subsequently, the Tolserol effect manifested itself in improving interpersonal relationships. There was some complaint on the part of children over the taste of the Tolserol. Recent experience with a new, related compound, Tolseram, indicates that it has the same effect but is more palatable.

It was surprising that Ambodryl, which is closely related to Benadryl, was of such little use therapeutically. One would suspect that the chemical modification reduced the therapeutic value of the compound for psychiatric purposes.

Several children displayed dizziness and dilatation of the pupils with Artane. The general usefulness of this drug appeared to be negligible. Rather, more children were adversely affected by Artane than any of the other drugs.

In view of the many favorable reports concerning the use of Serpasil, no explanation can be offered for the failure of this drug to benefit a significant number of children. Since the reports concerned adults essentially, it may be that Serpasil is not effective in children. We have, as yet, no experience with dosages higher than 3 mg., nor has the drug been administered intramuscularly.

In no instance where improvement was noticed could one say with certainty that any of the drugs had altered the basic psychopathology.

The pharmacological agents have an undoubted role in the management of children with psychiatric disorders, but they cannot be considered to be curative. They greatly help in the conduct of the ward and are a most useful adjunct in the program of a residential set-up.

Actually, the goal in drug therapy in children is not solely one of attaining agents which will subdue and pacify destructive and agitated children. Another problem is the procurement of drugs that will stimulate the withdrawn and autistic child, help the integration of the poorly coordinated child, and stimulate the development of the immature child. None of the drugs in the above series seems to have any stimulating effect such as seen in some children with benzedrine. The Tolserol did seem to improve the integration of the poorly coordinated child but, by no means, can it be considered completely satisfactory.

There is obviously great need for further research in specific drugs and also further work in the combination of known drugs; i.e., the combination of Benadryl and Thorazine would appear to give better results than either drug alone. However, having established the value of such agents, one can look forward to increased knowledge and effectiveness.

## Summary

1. One hundred and ninety-five children on a psychiatric ward have been treated with a series of six drugs: Benadryl, Tolserol, Artane, Ambodryl, Thorazine and Serpasil. A methodology is described for the study of such compounds that includes the use of placebo.

2. The Benadryl appears to have the best over-all effect and was particularly helpful in those children with primary behavior disorders displaying anxiety.

3. Thorazine was most beneficial for hyperkinetic, agitated, schizophrenic children.

4. Tolserol produced improvement in children with the diagnosis of organic brain disorder.

5. The results with Artane, Ambodryl and Serpasil did not appear to be significantly different from those obtained with placebo.

6. The drugs did not appear to alter the basic psychopathology found in the children.

7. Pharmacological agents have an indisputable role in the management of children in a psychiatric hospital setting.

8. Necessity for further research in this area is indicated.


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# STUDIES IN HUMAN CEREBRAL FUNCTION: THE EFFECTS OF MESCALINE AND LYSERGIC ACID ON CEREBRAL PROCESSES PERTINENT TO CREATIVE ACTIVITY[1,2]

LOUIS BERLIN, M.D., THOMAS GUTHRIE, M.D., ARTHUR WEIDER, PH.D., HELEN GOODELL, AND HAROLD G. WOLFF, M.D.

Four graphic artists of national prominence participated in experiments designed to ascertain whether the action of mescaline and lysergic acid would manifest itself in a unique manner in persons with their specially cultivated visual perceptions and skills, and to assess the effect of the agents upon their creativity.

The subjects ingested 400 to 700 mg. of mescaline or 50 gamma of lysergic acid in a single dose. Within 30 to 90 minutes after receiving the agent they began to have experiences comparable to those of non-artists under the influence of the drugs. They did not have a similar experience when given a placebo. They observed distortions of space as if the room swelled, the walls curved and small spaces became "cavernous". There was such a heightened awareness of environmental stimuli that one subject declared, "I felt like a mass—with my senses exposed to the raw environment."

Tactile perceptions were affected in such a manner that these subjects reported a greater sensitivity for objects they held, e.g., a piece of fur, a piece of paper or the brush as it was applied to the canvas. They became increasingly aware of sounds which now had a "chromatic" quality. Most striking were the effects of visual stimuli. Colors were described as having an added "purity", "vividness" and "brilliance". They reported that, short of their infrequent visual hallucinations of sparkling colored lights, they had had on previous occasions without the drug periods of heightened visual awareness while engaged in their work which approached those experienced during the action of the agent.

During the drug effect, sound, color and texture existed for the subjects as pure sensations, without esthetic value. Color and texture became "quite independent of meaning or significance"; a human skull seemed marvelously interesting in color and texture but had no meaning in terms of its human associations. The sounds of a violin seemed "ravishingly beautiful but it hardly occurred to me that what was being played was a composition." Colors floated away and became disembodied from the object to which they belonged. During these experiences the subjects were aware that this detachment of color and texture from the total context was "silly". Nevertheless, they stated that now for the first time they had the idea that perception could exist as an end in itself, independent of all human values.

During a period when they were most severely affected by the agents, three of the four subjects were disinclined to exploit their experiences or to mobilize their resources toward a productive goal. They reported that they did not want to concentrate on their work, but only wanted to "look and feel". The act of painting was now burdensome and fatiguing. The subjects acted as though they were incapable of sustained effort. However, one subject did paint with great fervor and excitement.

While under the influence of mescaline and lysergic acid, the subjects exhibited impairment of their highest integrative functions. They performed less efficiently on steadiness and tapping tests, Porteus mazes, the Purdue pegboard, the digit symbol and block design of the Wechsler-Bellevue Tests. Minute estimation was lengthened. Halstead's adaptation of the Seguin-Goddard form board was less rapidly done, and the board was less well remembered. In their original drawings and their copying of the Bender-Gestalt figures, there

[1] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

[2] From the Study Program in Human Health and the Ecology of Man, and the Departments of Medicine (Neurology) and Psychiatry, New York Hospital, Cornell Medical Center, New York.

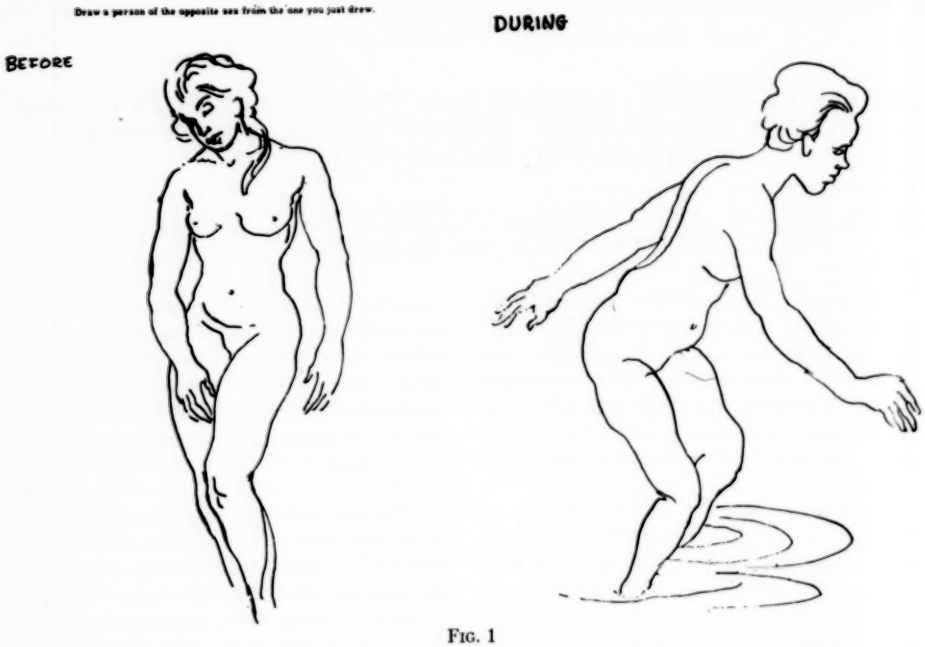


FIG. 1

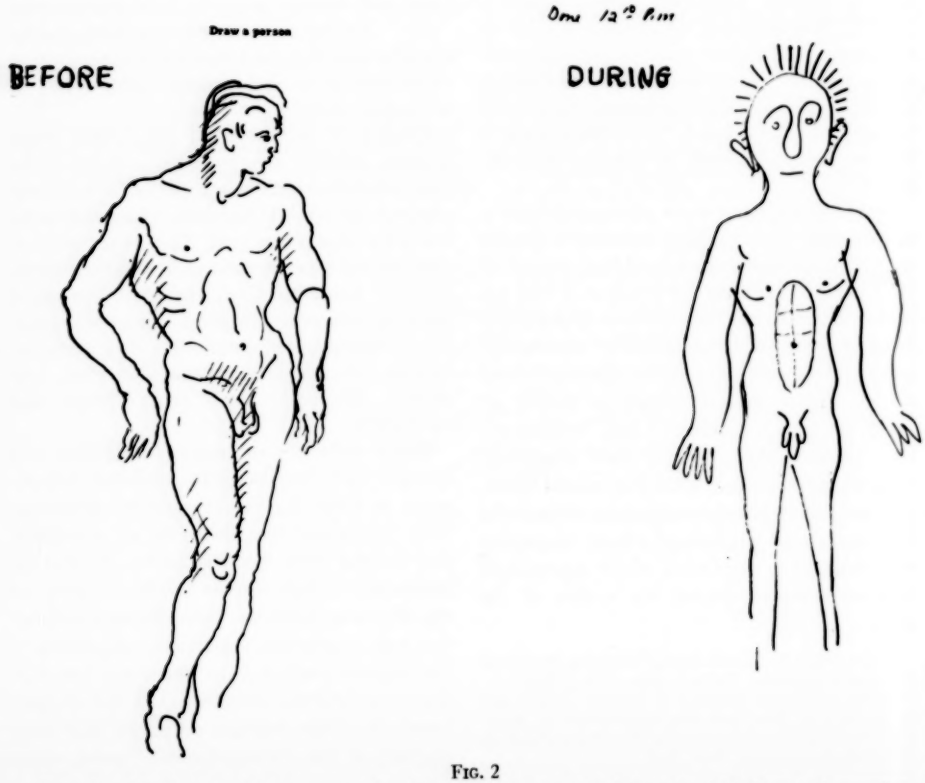


FIG. 2

FIGS. 1 and 2. Drawings by the same artist in the normal state and while under the influence of mescaline.

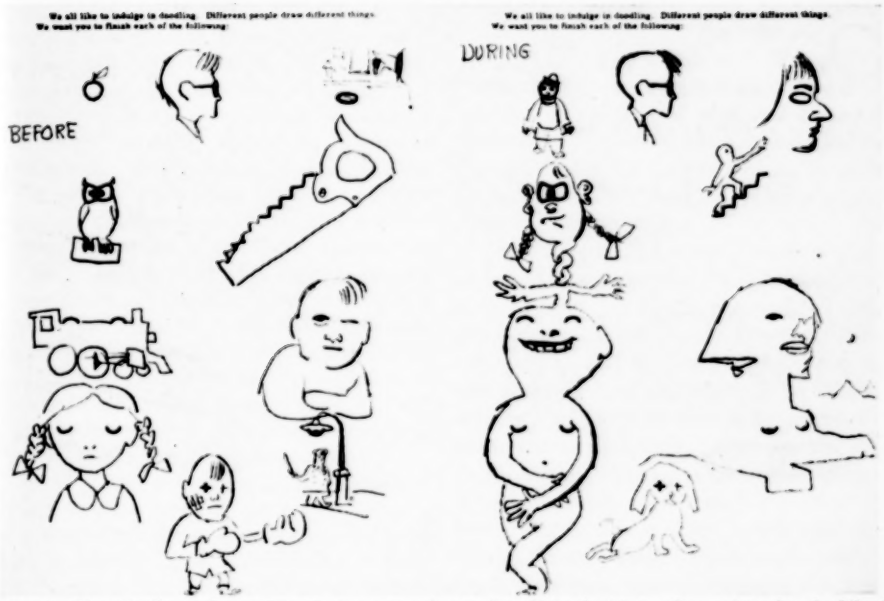


FIG. 3. "Doodling" as influenced by the ingestion of mescaline. Note the bizarre figures introduced while the artist was under the influence of mescaline.

were observed an unusual expansiveness and relaxation of controls. The five figures demonstrate this breakdown of restraint under the influence of mescaline and lysergic acid, as revealed by their drawings.

In figure 1, taken from the Draw-A-Person Test, the subject, under the influence of mescaline, showed greater freedom of movement as compared with a similar drawing done previously, but drew a figure with less precise detail and devoid of imagination.

The second of these drawings (fig. 2) by the same artist again demonstrated that during the drug effect there was an indifference to detail, and he drew a simple, crude, bizarre figure, unlike the man drawn when the artist was in the normal state.

The bizarre is evident in the third drawing (fig. 3), which is doodling performed by one of the subjects. Note that the figures became bizarre, expansive and freer when they were drawn while the subject was under the influence of the agent.

The next series of figures demonstrate the alterations in attitude and controls as reflected in drawings of the Bender-Gestalt figures.

In figure 4, there are apparent during drug effect a casualness and indifference to careful spacing and reproduction of the figures.

In figure 5, the expansive quality was so great that the subject could not reproduce all the figures on the same page.

When the subjects painted, they either altered their previous productions or produced new paintings, which were then adjudged by their peers, other qualified artists, to have heightened esthetic value. This improvement in their esthetic creativity may be explained by the following observations. The subjects became aware of "dead areas and dull colors" in their paintings and were able to modify them. There was a new feeling of unconcern about drawing in a "loose free way", and this loosening of restraint was evident in the size, freedom of line and brilliance of colors employed in their paintings. One artist who described her approach to painting as "indirect and tentative with many changes" felt "relaxed about the mistakes in drawing" and "could cope with them in due time" while under the influence of mescaline.

A fifth subject, a playwright, without the painters' capacity for visual fantasy, given 50

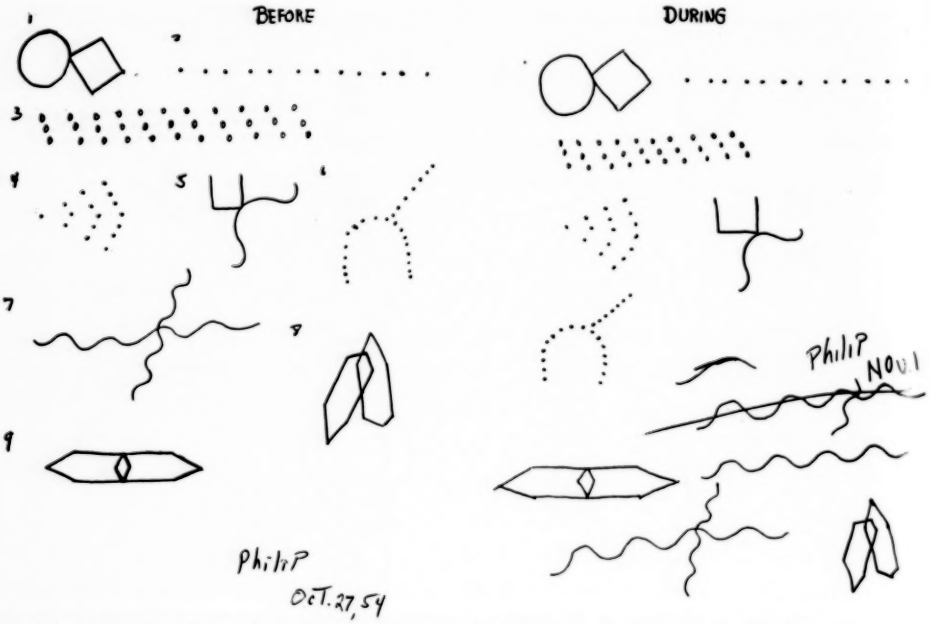


FIG. 4. Alterations in the drawings of the Bender-Gestalt figures drawn by an artist under the influence of mescaline.

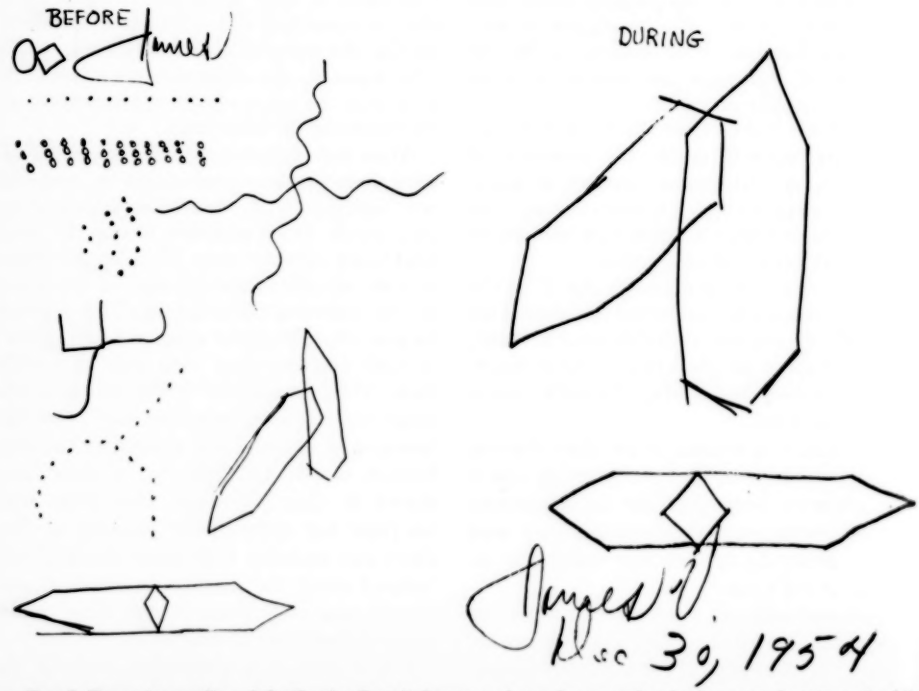


FIG. 5. Expansive quality of the Bender-Gestalt figures as drawn by an author in the normal state and while under the influence of lysergic acid.

gamma of lysergic acid, showed impairment of functions akin to those of the graphic artists. He experienced the same visual, auditory and tactile aberrations of sensation and found it "a great effort" to apply himself to any work. As he stated, "despite this extraordinary view of the natural world—you are removed from desire and left with an uncomfortable sense of negation and waste of self." For this author "all life" had gone out of a passage he had written previously. He attempted to work on a scene in one of his plays and found that now "human conflict or struggle was without meaning." During the period of detachment and indifference to human events while he was under the influence of the agent, he failed to attain his usual level of literary creativity.

Among these perceptive and imaginative persons, unaccustomed to the use of "drugs", the effects of lysergic acid and mescaline were indistinguishable. Those artists who took both agents could detect no major difference in their effect.


## Summary

The action of mescaline and lysergic acid was that of inhibition or depression of the usual regulated activities of the subjects. The four graphic artists who ingested these drugs had impairment of their highest integrative functions as described above.

They, nevertheless, created works of greater esthetic value appeal according to the panel of fellow artists, but this was associated with a relaxation of control in the execution of lines and employment of color, so that both color and line were freer and bolder. The effects on sensory function were such as to augment the perception of dull areas in their paintings, but detached the colors from their relationship to the whole esthetic structure. Furthermore, the benefits derived from these agents were offset by the difficulty these subjects had in mobilizing their perceptions and energies in the pursuit of creative art.

# AN EVALUATION OF THE CLINICAL SIGNIFICANCE OF RESERPINE[1]

J. S. TYHURST, M.D.,[2] AND A. RICHMAN, M.D.[3]

This paper is concerned with a brief review of several points we have felt to be of significance in our clinical experience so far with reserpine in psychiatric patients. Some preliminary impressions have already been reported (4, 6).

## Type of Patient

We have been working with an in-patient population, most of whom have been selected specifically because of a fairly severe degree of overactivity or agitation or because they presented problems in ward management and therapy. We have had little experience with chronic mental patients or with run-of-the-mill neurotic patients in an out-patient department. The material we have therefore allows us to make statements concerning overactivity, agitation and the treatment of hospital wards problems, but it is not suitable for making clear-cut statements regarding diagnostic specificity. In conformity with the experience of others, we have found that over-agitation and over-activity constitute a reasonable symptomatic indication for use of the drug, whereas the presence of considerable retardation or depression does not appear to be favorable. The working out of further indications, based on nomenclature, symptoms or psychodynamics, will take some time, a very large number of patients, and is an important area for future clinical exploration and definition. In this paper, we are concerned with a discussion of the clinical significance of the drug as used on the basis of these indications developed so far, and with in-patients on a hospital ward.

## Dosage and Duration of Treatment

Initially we were conservative with dosage but became bolder as no serious side effects developed, and as we attempted to use the drug with a wider range of patients. At present our regime consists of the initial administration of 10.5 mg. daily—7.5 mg. intramuscularly in three divided doses of 2.5 mg., and 3 mg. orally in three divided doses of 1.0 mg. Initially, we watch for somnolence, lassitude and decrease in agitation. If these do not occur, we raise the dosage until somnolence appears.

Generally speaking, it is our impression (a) that fairly high dosage should be used to start with, sufficiently high to produce somnolence, and (b) that lack of success with the drug can be due to a failure to use high enough initial doses. Treatment should be continued at a fairly high dose level until a useful clinical effect is observed and maintained, at which time the intramuscular administration can be gradually reduced and finally discontinued, the patient then being maintained on an oral dosage of about 3 mg. daily.

## Side Effects and Complications

We have observed the various side effects commonly noted (4, 6). We would like to draw attention to a more recent observation that treatment with reserpine appears to increase greatly the likelihood of serious complications when the patient is also on insulin coma. In a 5-month period, while 5 out of 6 reserpine-treated patients developed complications in insulin coma, only 5 out of 36 non-reserpine patients developed complications. The complications seen in reserpine-treated patients included 2 prolonged comas, 1 cyanosis, 1 increased sensitivity to insulin, and 1 death with respiratory arrest. The complications with non-reserpine patients were all prolonged comas. Although it may not be possible yet to establish a clear-cut physiological relationship

[1] Read at the Tenth Annual Convention of the Society of Biological Psychiatry, Chicago, Ill., June 12, 1955. From the Allan Memorial Institute, Royal Victoria Hospital, Montreal, Canada.

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between the reserpine treatment and the complications in coma, the greatly increased likelihood of complications would indicate that caution should be used in administering the drugs together. Furthermore, it is not clear just how long the delayed effects of reserpine in this instance are liable to appear after administration of the drug has been stopped.

### Daily Visiting of the Patient

We feel it is important for the physician to visit and examine the patient daily for reasons which reflect what should be done at these daily visits.

(a) Dosage must be established on the basis of a daily evaluation of the clinical status of the patient and should be adjusted daily. Individual variations in response to the drug seem to be marked, and a dosage that produces marked somnolence in one patient may produce no effects whatsoever in another. Individual observation is necessary to obtain the optimum effect for any particular patient from day to day. Thus, for good results, we believe it is necessary to observe the clinical status of the patient daily and to raise or lower the dosage of the drug accordingly, particularly in the *initial stages* of treatment. We have felt it is of much less value to place the patient on the drug at some initial dose and to leave him on this for a week or 10 days.

(b) A second reason for daily visiting is to reassure the patient regarding the various troublesome side effects such as rhinitis, trembling, feelings of lassitude and fatigue and the early and later stages of the extrapyramidal syndrome (4). These various physical side effects may produce a good deal of secondary anxiety and concern which may interfere with the effect of the drug in reducing agitation and over-activity. Some patients may react to the subjective sensations of lassitude and heaviness produced by the drug with the concern that they are losing their strength, are being rendered weak, and so on. Where preoccupation with strength, potency and self-esteem figure importantly in the patient's psychodynamics, these effects can lead to an anomalous increase in agitation which may be relieved by reassurance and psychotherapy or may cause the drug to be discontinued.

(c) Daily visiting is valuable for both diagnostic and psychotherapeutic purposes. With treatment, the clinical status of the patient often changes considerably from day to day, and these changes may be of considerable diagnostic significance. With a reduction of agitation and over-activity, the patient becomes more accessible, and, apart from overt symptomatology, it becomes possible to secure information from the patient that is of assistance in reaching a more complete diagnostic formulation including factors from the personal history and social environment. Again, the increase in accessibility and the reduction in agitation are often also accompanied by a definite need on the part of the patients to discuss their problems and symptoms with the staff. We have not seen so much "turbulence" as has been reported elsewhere (1, 2), and though our number of patients is small, we have felt that one reason for less disturbance with the drug may be due to daily visiting and reassurance regarding subjective effects.

### Clinical Significance

Finally, we would like to refer to the clinical significance of the drug in more general terms, and to introduce this with a story which seems relevant.

Just before the second World War, an allegorical book was written by a Polish writer about the possible future of Europe which was described as being in a state of decadence. Western civilization was said to be threatened in this imaginative account by an army from the East, a Sino-Mongolian army that dominated all the territory stretching from the Pacific to the Baltic. The situation as it develops further is described as follows:

> "(they) are unhappy because they have no faith and have no sense of meaning in their work. This atmosphere of decay and senselessness extends throughout the entire country. And, at that moment a great number of hawkers appear in the cities peddling Murti-Bing pills. Murti-Bing was a Mongolian philosopher who had succeeded in producing an organic means of transporting a "philosophy of life". This Murti-Bing "philosophy of life" . . . was contained in pills in an extremely condensed form. A man who used these pills changed completely. He became serene and happy. The problems he had struggled with until then suddenly appeared to be superficial and unimportant. He smiled indulgently at those who continued to worry about them . . . he lived in the midst of his compatriots

like a healthy individual surrounded by mad men. More and more people took the Murti-Bing cure and their resultant calm contrasted sharply with the nervousness of their environment." (3).

Although reserpine is also an ancient Asiatic remedy and does produce a state of serenity in a significant number of cases, it is no Murti-Bing pill. It does not contain a "philosophy of life" in organic form.

Its value is in producing symptomatic remission without many of the disturbing side effects produced by other forms of drug or physical treatment. This symptomatic improvement is not necessarily lasting after the administration of the drug is stopped. Persistence of symptomatic remission appears to depend, as we have already noted, upon the important question whether additional therapeutic activities had been provided while the drug was being administered. We have been able to identify two possible kinds of additional activity required. The first consists of the patient's own activities towards recovery[4] which may be postulated as coming into play as the drug serves to interrupt a symptom pattern which has become chronic, oscillating or autonomous.[5] The second consists of active psychotherapeutic intervention by the psychiatrist, both in terms of the patient's personality structure and in terms of dealing with problems in the patient's family and social situation (6).

Thus, one of the important points of significance is the opportunity for therapy that the symptomatic remission affords. The production of remission without memory loss, states of confusion, or lethargy makes it possible to secure a more complete picture of the patient's symptoms, personal history and life situation. Frequently, the need to observe a patient for a period of time or to secure further crucial background information is frustrated by the therapeutic and ward crisis that develops if active treatment is not instituted early. In our experience, the drug has permitted us to avoid this crisis in a significant number of patients and to secure more comprehensive formulations not only of presenting symptomatology, but also of important underlying symptoms and factors in the personal and social history. It is not so much that the drug itself produces the material in any sense, but that the patient is simply more accessible. We are then able to use this more comprehensive formulation in the development of a treatment plan that goes beyond the immediate symptomatic remission to psychotherapy and rehabilitation. It seems to us that a real shift in emphasis is becoming possible, for not only is the orientation of the treatment plan broadened, but there is characteristically an increased demand to solve problems of social and occupational rehabilitation as the discharge of the patient becomes a possibility.

The net effect of increasing the accessibility of the patient is to bring about a marked increase in the intensity of the relationship between doctor and patient and to focus attention upon the therapeutic resources of the hospital as a whole. This comes at a time when other developments are emphasizing the importance of the social environment and social structure in the hospital treatment setting (5).

The phrase "symptomatic remission" has been used here in discussing the significance of the drug. Some clarification of the phrase is required. Usually, the phrase actually refers to those features recognized by psychiatrists-in-hospital as "symptoms". As these symptoms are relieved, the psychiatrist is then encouraged to seek the discharge and social rehabilitation of the patient. With this, a host of problems present themselves, and in a comprehensive sense these further problems should also be thought of as "symptoms" of a total psychosocial disorder affecting the individual. The altered behavior, disordered thinking and disturbed mood are features the psychiatrist-in-hospital has generally recognized as "symptoms"—these are the "symptoms" he treats, and with their remission he speaks of improvement.

Thus, the term "remission" with regard to symptoms can be used legitimately in only a limited sense, a limitation that we will come to see more and more clearly as we are freed

[4] "The line between the spontaneous forces tending to recovery—what used to be called *vis medicatrix naturae*—and the effects of the physician's 'intervention' is impossible to draw with precision in a very large proportion of cases." "Social Structure and Dynamic Process: The Case of Modern Medical Practice" in: *The Social System*, by T. Parsons, Glencoe, Ill.: The Free Press, 1951, pages 449–450.

[5] This oscillatory behaviour may be one of the principal difficulties of feed-back systems. See, e.g., Tustin, A.: *Scient. Am., 187:* 48, 1952.

from our preoccupation with in-hospital symptomatology and as we come to review our notions of what constitutes mental disorder, going beyond the overt disturbance of function in the isolated individual to describe and formulate symptoms of his disturbance of function in his everyday social environment.

The use of this drug is bound to accelerate these trends: this is probably a point of major significance. It will lead to increasing attention to psychotherapy and the therapeutic milieu of the hospital, to increased demand for staff rather than less, and to focusing more attention upon the relevant social environment of the patient outside the hospital in terms of the description both of "symptoms" and of etiology.

Perhaps, to take one step further, the drugs, by the shift of focus that they appear to encourage, will eventually render themselves obsolete as we become sufficiently skilled in dealing with the underlying problems of psychosocial conflict and disorder rather than with those derived manifestations now referred to in the phrase "symptomatic remission". Many of the problems in symptomatic treatment which we face today may well be bypassed in the same way that the problems in the symptomatic treatment of typhoid, smallpox or poliomyelitis have been by-passed by the increase in our preventive knowledge.

The Serpasil—Ciba used was furnished by the kindness of Dr. C. Walter Murphy, Ciba Limited, Montreal.

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6. Tyhurst, J. S., and Richman, A.: Clinical experience with psychiatric patients on reserpine: preliminary impressions. *Canad. M. A. J., 72:* 458–459, 1955

# SUMMARY OF PAPERS ON DRUGS AFFECTING BEHAVIOR[1]

MAX RINKEL, M.D.

The principal drugs which affect human behavior are: Mescaline, the diethylamide of d-lysergic acid (LSD), chlorpromazine (Thorazine), reserpine (Serpasil), Meratran and its isomer, Frenquel. Physiological, theoretical, clinical and psychopathological considerations, resulting from the use and study of these drugs, were reported in 14 papers at this meeting which has been characterized by the usual high standard of scientific presentation. It is impossible, summarizing 14 scientific papers, to do justice to each individual author and the discussants who have critically evaluated and appraised each paper.

With this advance apology, the wealth of the data collected and theories formulated may be summarized as follows: The antagonistic, cumulative or synergistic effect of various drugs was made explicit by studies in rabbits and man. Rinaldi and Himwich, who have contributed considerably to the elucidation of the physiology of these drugs by linking their action with the mesodiencephalic activating system, reported that α-4-piperidyl carbinol hydrochloride is specific in the rabbit for the restoration of normal electroencephalographic patterns from the changes produced by LSD and mescaline. Dice, Bagchi and Waggoner discussed encephalographic and other observations of the early and cumulative effects of reserpine that was administered to psychotic and brain damaged adults and children. The potentiating action of chlorpromazine on barbiturates and narcotics was demonstrated and recorded electroencephalographically by Sadove, Balagot and Reyes, who used rabbits for their experiments. They reported a definite cumulative effect for chlorpromazine and barbiturates, but a somewhat doubtful one for opiates or opioids.

Progress in the pharmacology of LSD was reported by Dr. Hodge and his associates. Their studies were done on rats, and a radioactive carbon-marked molecule of LSD was used. The history of this research started at the wedding of the son of a mutual friend of mine and Dr. Hodge. At this wedding, I approached Dr. Hodge and asked him to investigate the pharmacology of LSD with an isotope-marked molecule. At the Boston Psychopathic Hospital, we had outlined this study in our very first LSD project which we submitted in 1949 to the council for approval. Since no isotope-labelled LSD existed at the time, Dr. Hodge graciously accepted the task of producing a radioactive molecule to study the pharmacology of LSD. We then approached the Sandoz Chemical Company to provide us with the necessary quantity of LSD and learned that Professor Rothlin had already accomplished the task of labelling LSD with $C_{14}$. Dr. Rothlin's cooperation was immediately secured, and the Sandoz radioactive LSD was used by the Rochester group of Boyd, Bonner, Slater and Hodge in their pharmacological studies on LSD. One of the outstanding results of this research was the minimal concentration of LSD in the brain, as compared to the large concentrations in the liver, kidneys and intestinal content. Although the meaning of these findings is still not fully understood, the continuance of these studies will bring to light new facts and more problems, and eventually a better understanding of the chemical causes of the change in behavior.

Marrazzi and Hart uncovered the fact that the chemically and functionally related series of adrenaline, amphetamine and mescaline, and also the more powerful diethylamide of d-lysergic acid inhibit synapses in the visual cortex. On the basis of this observation, they postulate that cerebral synaptic inhibition plays a part in the action of hallucinogens. This action is either direct, by disruption of normal patterns of synaptic activity responsible for behavior, or indirect, by inhibiting normal restraints. This inhibition releases aberrant patterns of activity, which means an alteration in the balance between cholinergic excitation and andrenergic inhibition at susceptible cerebral responses.

Hoffer and Osmond, whose work in experi-

[1] Read before the Tenth Annual Meeting, Society of Biological Psychiatry, Chicago, June 11–12, 1955.

mental psychosis is well known, suggest the theory that Schizophrenia is an autonomic disease characterized by the two basic conditions: increased parasympathetic activity and increased concentration of indole.

H. Holland De Jong demonstrated with the aid of a motion picture that bulbocapnine is capable of inducing stupor in man.

Seven clinical papers reported on the therapeutic use of chlorpromazine and reserpine, individually or combined, or in combination with mescaline. Hoch used chlorpromazine (Thorazine) on in-patients and office patients and also reported the counteractive effects of this drug on the experimentally-produced psychoses. Bennett, Ford and Turk used either chlorpromazine or reserpine in a random selection of private psychiatric patients, and Barsa and Kline reported on the use of combined reserpine and chlorpromazine in the treatment of disturbed psychotics. Thorazine and reserpine were used by Freedman, Effron and Bender in children with psychiatric illness, and the unusual combination of mescaline-chlorpromazine was used by Denber and Merlis in the treatment of patients with various psychiatric diagnoses. Their technique was to inject intravenously 0.5 gm. of mescaline sulfate which brought out unconscious conflicts, severe tension and anxiety, which was then controlled by the intramuscular injection of 50 mg. of chlorpromazine. It is gratifying to note that all authors used strict controls, double blind methods, and placebos and were moderate in their claims of success in contrast to the early publications about these drugs. Fabing reported the effects of a new drug called Frenquel, which has no meaning but that the name qualifies for patent. It is the 4-piperidyl isomer of Meratran about which Fabing has reported in previous papers. It is of interest that Frenquel, according to Fabing, blocks or aborts experimental LSD and mescaline psychosis.

A paper of special interest was presented by Berlin, Guthrie, Weider and Wolff. They gave mescaline and LSD to 4 painters of national prominence and to one playwright to ascertain whether the action of the agent would manifest itself in an unusual manner and to assess the effect of the agent upon their creativeness. It seems to me that the most pertinent result was a decline of initiative of the painters, which offset the effects of augmented perceptions and reactions. There also was a decline of literary creativeness in the playwright who received LSD. The experiences of these authors coincide with those of Benda and myself when we gave mescaline and, on another occasion, LSD to a nationally-known contemporary painter who showed a progressive disintegration in his drawings though each line showed the superior craftsman in his art.

If we ask ourselves what the meaning is of the factual observations, the hypotheses and theories, the restrained but euphemistic clinical reports that have been presented here today, one cannot help but acknowledge that the advances in chemistry, especially the synthesis of new behavior-affecting drugs, have led to a change in psychiatric concepts, have opened the possibility, however small, of treating psychotic patients outside of a mental hospital, in the office or at home, and no doubt will materially influence the construction of new mental hospitals as open day-hospitals, in contrast to the custodial hospitals of the past. A new era in psychiatry is coming in which mental illness will be considered like any other illness, and superstition, shame and prejudice will be remembered only by historians.

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# BOOK NOTES AND REVIEWS

Books received are acknowledged and given a brief description in this section. Selections serving a variety of interests will be made from these for a more extensive review as far as space will allow.

## BOOK NOTES

*Krieg, W. J. S.*, BRAIN MECHANISMS IN DIACHROME. [Evanston, Illinois: Brain Books, pp. 188 and 55 illustrations, 1955, $7.00 ($6.00 per ten or more copies.)]

The author of this unique book is Professor of Anatomy in the Northwestern University Medical School in Chicago. He is the author of outstanding neuroanatomic books and articles which have been very useful to both students and instructors in this field. The present book presents the structure and function of the nervous system in a clear, simplified way to serve a wide variety of students from the college level on through the professions concerned with neuroanatomic matters.

The major portion of the book deals with the cerebral cortex with proper emphasis on its importance, but the sensory and motor systems, the histology of the various units, the tracts, the cerebellum and the autonomic nervous system are given an excellent presentation and review.

The book has some special features. In a front pocket there is a multicolored series of drawings of the human brain placed on transparent sheets with the various nuclei and fiber tracts having consistent colors and numbers throughout for easy identification in the text. This "diachrome" allows the student to dissect the layers of the brain from either the medial or lateral method. In a back pocket there are eight illustrations in black and white on the reconstruction of the rat brain.

Most of the illustrations are by the author and are well reproduced. The text throughout is very readable in view of the complexity of the subject. It is a scholarly contribution and merits a place of prominence in the educational institutions.

*Reed, S. C.*, COUNSELING IN MEDICAL GENETICS. [Philadelphia and London: W. B. Saunders Co., pp. 268, 1955, $4.00]

The desirability of a book of information sufficiently reliable to guide physicians who are called upon frequently to give practical advice to would-be parents on important genetic matters, is beyond question. The author, a well recognized geneticist, has here presented his method of counseling in this field and has discussed the available information that has accrued from the study of twins, various anatomic malformations, congenital heart disease, mental deficiency, blood genetics, disputed paternity, convulsions, tuberculosis and some psychoses and several other disorders with hereditary components.

In some of the conditions described the genetic component is not clear, the descriptions are often inadequate and disappointing and there are numerous controversial issues, but despite these defects, the book contains a good deal of useful information and is well worth reading. The thoughtful physician will scrutinize the text and accept for counseling whatever seems to be well established and applicable, since there is no little responsibility involved in advising families regarding factors that may change their entire life plan.

There are twenty-nine chapters, an appendix giving definitions of types of inheritance and frequency of disorders, a list of bibliographic references and an adequate index.

*Devereux, George*, A STUDY OF ABORTION IN PRIMITIVE SOCIETIES. [New York: The Julian Press, Inc., pp. 394, 1955, $6.50.]

The subtitle of this investigation is "A topological, distributional and dynamic analysis of the prevention of birth in 400 pre-industrial societies", and its author is a widely known psychiatrically oriented anthropologist and ethnologist, who has spent years in field work among the primitive or "belated" peoples in several parts of the world.

The study is presented in four parts. Part

One: Topology, deals with motivation, the alternatives to abortion, the frequency, time, techniques and physical consequences of the procedure and also describes the status of the aborted fetus, the abortionist, the attitudes and the various social actions. Part Two discusses the relationship of the culture and the unconscious processes, and Part Three presents the source material. Part Four consists of the tabulation of traits. There is a bibliography, a subject index, an author index and an index of ethnic groups and localities.

The work as a whole is extremely interesting, thought provoking and inviting to additional research, but it is a difficult one to review and summarize in a brief account. Here one finds a detailed description of the unconscious motivations of abortion in its many ramifications. It is a scholarly and original contribution, valuable both from the historical and psychological viewpoints, representing faithful and intensive research which will enrich the library of any psychiatrist or anthropologist with active psychological interests.

*McIlwain, H.*, Biochemistry and the Central Nervous System. [Boston: Little, Brown and Company, pp. 273 and 43 illustrations, 1955, $9.50.]

New books presenting research on the biochemistry of the brain are always welcome to those who still consider the condition of the brain as having some bearing on psychiatric problems. The author of this text is an active worker and teacher in this field in the University of London and the Institute of Psychiatry, Maudsley Hospital and his selection of topics and their contents is most reliable and rewarding to those who have some orientation and interest in neurochemistry. As a whole it will serve as a concise introduction to the study of brain metabolism for those students who may have a flair for the dynamic aspects of biochemistry.

Among the fourteen chapters there are those on pyruvate metabolism, amino acids, vitamins, lipids, depressants and excitants, on developmental aspects in terms of chemical and enzymic composition, and on cytochemical and histochemical aspects of cerebral functioning.

The frequent references to pharmacology, endocrinology, chemical pathology, mental disorders and other allied disciplines show the overlapping and also the possible integration of many research areas for future study. The text is well documented and adequately indexed. It deserves an extensive reading.

*Minz, Bruno*, The Role of Humoral Agents in Nervous Activity. [Springfield, Ill.: Charles C Thomas, pp. 230, 50 figures, 1955, $7.75.]

The author of this monograph is a Research Professor in the Department of General Physiology of the Sorbonne, Paris. The text is based on a series of seminars delivered in the Department of Pharmacology at the University of Illinois, Chicago. The author himself has made original contributions in the field of neurohumoral transmission and he is fully aware of the problems that remain to be solved by additional research.

There are five chapters, the first being devoted to a historical account of the origin of the concept of neurohumoral transmission. The second chapter presents the experimental evidence for humoral transmission in the autonomic nervous system, the third describes the cholinergic mechanisms, the fourth gives an account of adrenergic mechanisms and the fifth chapter is concerned with the role of, chiefly, acetylcholine in the activity of the central nervous system. A liberal list of pertinent references is presented at the end of each chapter.

The book is clearly written and easily read being a masterly exposition of complicated mechanisms and issues brought together in a way which should serve well all students of neurophysiology and clinicians who are in need of improving their orientation in this important field which is bound to expand with future investigations.

*Kreig, W. J. S.*, Connections of the Frontal Cortex of the Monkey. [Springfield, Ill.: Charles C Thomas, pp. xi + 299: 187 figures. 1954, $10.50.]

This volume presents an analysis, reconstruction and a synthesis of the anatomical results of 70 discrete, localized lesions in various areas of the frontal cortex of Macaca mulatta monkeys. The mass of detailed ob-

servations and recordings represented in this account is truly astonishing, and it is probable that nothing so extensive and complete of this particular area has ever been done before.

The topographical nomenclature is that of Brodmann and the Vogts for the principal areas, but the author has described a number of subareas and other parts. The Marchi method was used throughout the studies, and the findings from serial sections are shown in three dimential reconstructions.

The illustrations are drawn by the author who in this book as well as in his other publications, demonstrates a unique ability as an illustrator of neuroanatomic structures. Investigations of this nature and scope in comparative neurology will in time reveal the extent of their contribution to the understanding of the human cortex and other brain structures, the sum total of which constitute the organ of the mind.

The book deserves careful study by both laboratory specialists and chemical workers in the neurological disciplines. They will find a clear scholarly presentation of informative material gained by intensive patient research. The publishers have also done an excellent job of bookmaking.

## BOOK REVIEWS

*Ey, Henri (Ed.)*, ENCYCLOPEDIE MEDICO-CHIRURGICALE. PSYCHIATRIE. [18 rue Seguier, Paris, 1955]

An admirable publication on psychiatry came out in France as part of a general medico-surgical encyclopedia. Henri Ey is the editor of the psychiatric part which is the most comprehensive work on psychiatry since the time between the two world wars. These three big volumes and the simultaneous preparation of a similar Italian encyclopedia show the enormous effort on the part of European psychiatrists to arrive at an integration of our present knowledge.

It is impossible to review a work by so many different authors. However, a few words should be said about the introduction by Henri Ey himself. He presents an extremely clear and extensive history of psychiatry which is followed by the concepts of the author himself who has a great following in France and other countries. He calls his concept an organodynamic one, and sees men like Pierre Janet, Eugene Bleuler, Adolf Meyer, Henri Claude and Ernst Kretschmer as those who have inspired this trend. He considers mental pathology as caused by a disorganization. Mental pathology cannot be satisfied to see in mental illness mechanical accidents, i.e. cerebral accidents, nor simple reactions to situations. It must rather take mental illness as a disorganization of the psychic being. This organodynamic approach which is sometimes called "Neo-Jacksonian" places psychiatry into the field of medical sciences having man as its object, man reduced in his liberty and humanity and not only in his vitality.

These concepts were not imposed on any of the collaborators of the volumes dedicated to psychiatry. They are a comprehensive account of present-day psychiatry. Differences in French and other classifications do not diminish the value of this treatise.

A separate annex to the psychiatric part of the encyclopedia deals with "Psychiatry in the World." It is written by prominent psychiatrists from various countries and deals with trends, doctrines as well as problems of professional organization, hospital matters and legal aspects in the respective countries. This annex of 78 pages contains a wealth of valuable information for those who are interested in differences in the approach to psychiatric problems in different countries.

This amazing addition to the psychiatric literature gives the most comprehensive information on present-day psychiatry available anywhere.

LOTHAR B. KALINOWSKY

# BOOKS RECEIVED FOR REVIEW

## October, 1955

BASH, K. W. Lehrbuch der Allgemeinen Psychopathologie. Georg Thieme Verlag, Stuttgart, Germany.

DE JONG, J. G. Y. Dystrophia Myotonica Paramyotonia and Myotonia Congenita. Koninklijke Van Gorcum & Comp., Assen, Netherlands.

DELAY, J., PICHOT, P., AND PERSE, J. Méthodes Psychométriques en Clinique, Tests Mentaux et Interprétation. Masson & Cie, Editeurs, Paris, France.

LEMKAU, PAUL V. Mental Hygiene in Public Health. Second Edition. McGraw-Hill Book Co., Inc., New York, N. Y.

O'SULLIVAN, EAMON N. M. Textbook of Occupational Therapy. Philosophical Library, Inc., New York, N. Y.

SCHAFFNER, BERTRAM (Ed.) Group Processes, Transactions of the First Conference—September 26, 27, 28, 29 and 30, 1954. The Josiah Macy, Jr. Foundation, Packanack Lake, N. J.

ROBACK, A. A. Present-Day Psychology. Philosophical Library, Inc., New York, N. Y

# NOTES AND NEWS

In January 1956 the American Psychological Association will initiate publication of a new monthly journal entitled *Contemporary Psychology: A Journal of Reviews*. Edwin G. Boring of Harvard University has been named editor of the journal, with Adolph Manoil of Park College serving as film editor. A group of 26 consultants in the specialized fields of psychology will assist Dr. Boring.

It is the aim of *Contemporary Psychology* to provide critical reviews of books in the broad field of psychology and related sciences, thus providing more comprehensive coverage of the psychological literature. Specialized book reviews formerly appearing in the APA journals *Psychological Bulletin*, *Journal of Applied Psychology*, *Journal of Abnormal and Social Psychology*, and *Journal of Consulting Psychology* will be concentrated in the new journal.

On November 29th, 1955 Dr. Jules H. Masserman, Professor of Psychiatry and Neurology at Northwestern University, returned from a six-week lecture tour through South America under the auspices of the World Health Organization. During this trip he addressed the faculties of the Universities and various scientific societies at Rio de Janeiro, Sao Paulo, Montevideo, Buenos Aires, Santiago, Lima, Panama, Costa Rica and El Salvador, as well as the psychoanalytic groups in South America. Dr. Masserman will report on the teaching and practice of psychiatry to the World Health Organization and other appropriate agencies.

A biometrics unit, a research group which will bring biometric methods to bear on the problems of psychiatry, will be added to the New York State Department of Mental Hygiene overall organization on February 1, it was announced today by Dr. Paul H. Hoch, Commissioner of Mental Hygiene. The unit will be located at the New York State Psychiatric Institute, 722 West 168th St., New York City.

The new section is being set up under the department's new nine-point program, Dr. Hoch said, to provide proper scientific statistical evaluation of the department's current and projected research. Dr. Joseph Zubin, principal research scientist (biometrics), will be in charge of the new unit.

Biometrics is the mathematical analysis of biological data, Dr. Hoch explained. In the field of mental disorders, it provides techniques and methods for assaying the physical, physiological, psychological and social characteristics of individual and groups of mental patients. It will be particularly helpful in screening, diagnosis and prognosis, Dr. Hoch added.

The work of the division will be carried on partly in the offices of the Institute, but will be basically state hospital centered, Commissioner Hoch declared. The unit will work directly with the patients and their records and the personnel and procedures involved in the project under study.

Dr. Philip M. Margolis, formerly instructor in the Department of Psychiatry, University of Minnesota, has been appointed assistant professor of psychiatry at the University of Chicago Clinics, according to announcement by Dr. L. T. Coggeshall, dean of the University's Division of Biological Sciences, and Dr. C. Knight Aldrich, head of the Department of Psychiatry.

Forty-two new research grants have been awarded by the National Institute of Mental Health upon recommendation of the National Advisory Mental Health Council at its June and November 1955 meetings. The total amount awarded in new grants was $674,149.

The Advisory Council at the June and November meetings also approved the continuation of one hundred two research grants, amounting to $1,713,272. The favorable recommendation of the Advisory Council qualifies these grants for continued support by the National Institute of Mental Health.

A grant for $13,000 to study why some children have difficulty in reading was awarded

by the Illinois state department of welfare to the Dyslexia Memorial institute at the Northwestern University Medical Center. Dyslexia is the medical term for difficulty in reading.

The research will continue the institute's investigations into what factors actually cause the children's inability to read properly and what can be done to treat the child.

The seventh lecture in the Sixth Annual North Shore Health Resort Lecture Series on "Psychiatric Problems in Medical Practice" will be held at our hospital, 225 Sheridan Road in Winnetka, Illinois on Wednesday, April 4, 1956 at 8:00 P.M. *The Management of Overeating, Overdrinking and Oversmoking* will be discussed by Leo H. Bartemeier, M.D., Medical Director, Seton Psychiatric Institute, Baltimore; Teaching Analyst, Washington Psychoanalytic Institute, Clinical Professor of Psychiatry, Georgetown University Medical School, Washington, D. C., Past President, American Psychiatric Association.

The effect of alcohol on the ability of a person to cope with emotional problems will be studied at Northwestern University medical school. The department of neurology and psychiatry received a grant for $26,000 from the Illinois state department of welfare to begin the study as the initial step in a broad research program on narcotic addiction.

The research will be under the direction of Drs. G. K. Yacorzynski, professor, and Harvey Nash, associate.

The Veterans Administration Hospital, Lyons, New Jersey, has available residencies in Psychiatry for a one to three year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers as well as an Annual Institute at this hospital. Training may commence at any time.

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## EASTERN PSYCHIATRIC RESEARCH ASSOCIATION

This is the name of a newly organized association of psychiatrists chartered in New York State. The first President is David Impastato, M.D., of New York, N. Y. Vice President is Leo Alexander, M.D., of Boston, and Theodore R. Robie, M.D., of East Orange, is Secretary-Treasurer.

The protocol of this new organization's aims and purposes includes the following: "To initiate, encourage and foster research in psychiatry and related fields of medicine . . . to stimulate scientific study and research into the nature and development of human behavior; to organize and coordinate public and private research and efforts in the application of sound principles of psychiatric knowledge . . . to encourage the exchange of scientific knowledge and information in all fields of medicine and especially in the field of psychiatry and mental hygiene".

The Association will hold four meetings per year, including the annual meeting in October. At that meeting, an incentive prize will be awarded for the presentation of the best scientific report.

Members of the Executive Committee are William L. Holt, M.D., Albany, N. Y., Joseph L. Epstein, M.D., Katonah, N. Y., Emrich Friedman, M.D., Albany, N. Y., H. B. Lang, M.D., Albany, N. Y.

For further information, address Theodore R. Robie, M.D., Secy.-Treas., 676 Park Avenue, East Orange, N. J. Official transactions will be published in "Diseases of the Nervous System".